



Consommation
et Corporations Canada

Consumer and
Corporate Affairs Canada

Bureau des brevets

Patent Office

Ottawa, Canada
K1A 0C9

(11)	(C)	1,311,201
(21)		563,635
(22)		1988/04/08
(45)		1992/12/08
(52)		195-1.12
C.L. CR.		167-202
		260-229

(51) INTL.CL.⁵ C07H-19/16; C07D-405/14; A61K-31/70

(19) (CA) **CANADIAN PATENT** (12)

(54) Desazapurine-Nucleoside Derivatives, Processes for the Preparation Thereof, Pharmaceutical Compositions Containing them and the Use Thereof for Nucleic Acid Sequencing and as Antiviral Agents

(72) Seela, Frank , Germany (Federal Republic of)
Muth, Heinz-Peter , Germany (Federal Republic of)
Kaiser, Klaus , Germany (Federal Republic of)
Bourgeois, Werner , Germany (Federal Republic of)
Mühlegger, Klaus , Germany (Federal Republic of)
Von Der Eltz, Herbert , Germany (Federal Republic of)
Batz, Hans-Georg , Germany (Federal Republic of)

(73) Boehringer Mannheim GmbH , Germany (Federal Republic of)

(30) (DE) Germany (Federal Republic of) S.N. P 37 12 280.0
1987/04/10
(DE) Germany (Federal Republic of) S.N. P 37 39 366.9
1987/11/20

(57) 29 Claims

NO DRAWING

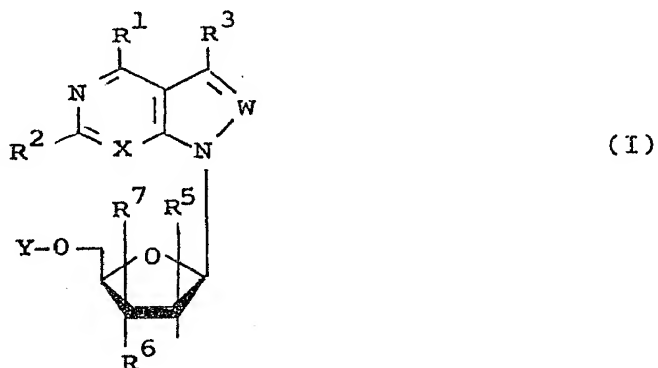
Canada

ABSTRACT

Desazapurine-nucleoside derivatives, processes for the
preparation thereof, pharmaceutical compositions
containing them and the use thereof for nucleic acid
sequencing and as antiviral agents

5

The present invention provides desazapurine-nucleoside derivatives of the general formula:-



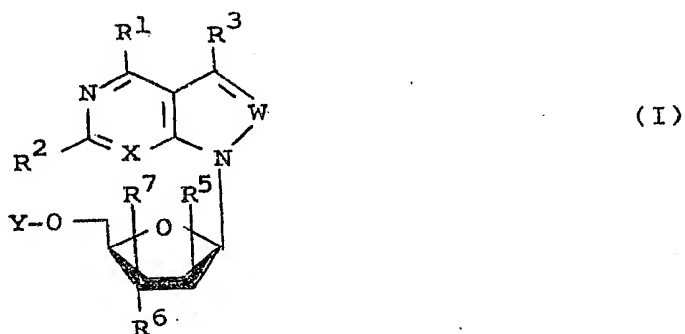
wherein X is a nitrogen atom or a methine radical, W is
10 a nitrogen atom or a $\geq C-R^4$ radical, R^1 , R^2 , R^3 and R^4 ,
which can be the same or different, are hydrogen or
halogen atoms, hydroxyl or mercapto groups, lower alkyl,
lower alkylthio, lower alkoxy, aralkyl, aralkoxy or
aryloxy radicals or amino groups optionally substituted
15 once or twice, R^5 is a hydrogen atom or a hydroxyl group,
 R^6 and R^7 are each hydrogen atoms or one of them is a
halogen atom or a cyano or azido group or an amino group
optionally substituted once or twice, whereby one of
 R^6 and R^7 can also be a hydroxyl group when X is a
20 methine radical and, in addition, R^5 and R^7 can together

533635 (2)

also represent a further valency bond between C-2' and C-3' and is a hydrogen atom or a mono-, di- or tri-phosphate group, as well as the tautomers and salts thereof and nucleic acids which contain one or more compounds of general formula (I) as structural components; these new compounds are useful for nucleic acid sequencing and as antiviral agents.

The present invention is concerned with new des-azapurine-nucleoside derivatives, processes for the preparation thereof, as well as the use thereof in the sequencing of nucleic acids, and also as anti-viral agents.

The new desazapurine-nucleoside derivatives according to the present invention are compounds of the general formula:-



- wherein X is a nitrogen atom or a methine group, W is a nitrogen atom or a $\geq C-R^4$ radical, R^1 , R^2 , R^3 and R^4 , which can be the same or different, are hydrogen or halogen atoms, hydroxyl or mercapto groups, lower alkyl, lower alkylthio, lower alkoxy, aralkyl, aralkoxy or aryloxy radicals or amino groups optionally substituted once or twice, R^5 is a hydrogen atom or a hydroxyl group and R^6 and R^7 are each hydrogen atoms or one of them is a halogen atom or a cyano or azido group or an amino group optionally substituted once or twice, whereby one of R^6 and R^7 can also be a hydroxyl group when X is a methine radical and, in addition, R^5 and R^7 can together



represent a further valency bond between C-2' and C-3' and Y is a hydrogen atom or a mono-, di- or triphosphate group, as well as the tautomers and salts thereof and nucleic acids which contain compounds of general
5 formula I as structural components.

The lower alkyl radicals in the definition of the substituents R^1 , R^2 , R^3 and R^4 can be saturated or unsaturated, straight-chained or branched and contain up to 7 and preferably up to 4 carbon atoms. This
10 definition of the alkyl radicals also applies to the alkyl moieties which occur in the definitions of the lower alkylthio and lower alkoxy radicals. The methyl and ethyl radicals are quite especially preferred.

By halogen in the definition of the substituents
15 R^1 , R^2 , R^3 , R^4 , R^6 and R^7 are to be understood fluorine, chlorine, bromine and iodine.

The aralkyl and aralkoxy radicals in the definitions of the substituents R^1 , R^2 , R^3 and R^4 contain an alkyl moiety with up to 5 and preferably
20 with up to 3 carbon atoms which are substituted one or more times with an aryl moiety suitably of 6 to 10 carbon atoms, for example, a phenyl or naphthyl radical. The aromatic radicals can, in turn, be substituted one or more times by an alkyl or alkoxy radical. The benzyl radical is especially preferred.

The aryl moiety of the aryloxy radical in the definition of R^1 , R^2 , R^3 and R^4 , suitably has 6 to 10 carbon atoms, the phenyloxy radical being especially preferred which can optionally be substituted one or more times by further substituents, for example, nitro groups and alkyl and alkoxy radicals.

10 The amino group occurring in the definition of R^1 , R^2 , R^3 , R^4 , R^6 and R^7 , which can optionally be substituted once or twice, contains, as possible substituents, preferably alkyl radicals with up to 5 and preferably up to 3 carbon atoms which, in turn, can be substituted by lower alkoxy radicals, halogen atoms or amino groups optionally substituted once or twice. These substituents can also represent an aralkyl radical with an alkyl moiety of up to 5, preferably up to 3 carbon atoms and an aryl moiety of 6 to 10 carbon atoms. The two nitrogen substituents can together also represent an alkylidene radical and preferably a methylenidene radical which, in turn, 20 can be substituted by lower alkoxy, substituted amino groups or halogen atoms. A quite especially preferred substituent of this kind is the dimethylamino-methylenidene radical.

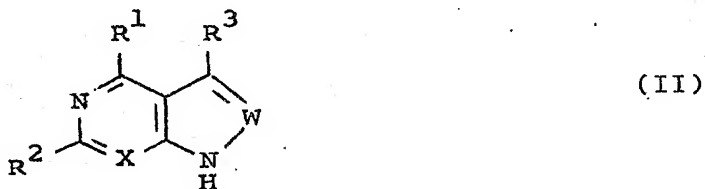
The monophosphate group is the $-\text{PO}(\text{OH})_2$ group, the diphosphate group is the $-\text{P}_2\text{O}_3(\text{OH})_3$ group and the triphosphate group is the $\text{P}_3\text{O}_5(\text{OH})_4$ group.

As possible salts, there are especially preferred the alkali metal, alkaline earth metal and ammonium salts of the phosphate groups. The alkaline earth metal salts are especially the magnesium and calcium salts. By ammonium salts, according to the present invention there are to be understood salts which contain the ammonium ion which can be substituted up to four times by alkyl radicals containing up to 4 carbon atoms and/or by aralkyl radicals, preferably the benzyl radical. The

substituents can hereby be the same or different. The salts of the phosphates can be converted in known manner into the free acids.

The compounds of general formula I can contain
 5 basic groups, especially amino groups, which can be converted into acid addition salts with appropriate acids. As acids for this purpose, there can be used, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic
 10 acid, tartaric acid, citric acid, lactic acid, maleic acid and methanesulphonic acid.

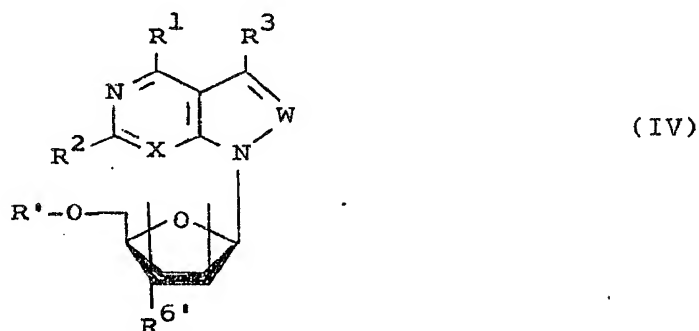
The compounds of general formula I are new. They can be prepared analogously to known, related compounds. For the preparation of the compounds of general formula
 15 I, a process has proved to be especially preferred in which a compound of the general formula:-



in which X, W, R¹, R² and R³ have the same meanings as above, is reacted with a compound of the general formula:-



in which R^5 has the above-given meaning, $R^{6'}$ and $R^{7'}$ each represent hydrogen atoms or one of these two symbols represents an azido group or a hydroxyl group protected by an oxygen protection group, R' is an oxygen protection group and Z is a reactive group, to give a compound of the general formula:-



in which X, W, R^1 , R^2 , R^3 , R^5 , $R^{6'}$, $R^{7'}$ and R' have the above-given meanings, and oxygen protective groups possibly present are split off and thereafter a compound thus obtained, in which R^6 or R^7 is a hydroxyl group, after selective protection of the 5'-hydroxyl group, is optionally converted with a halide, cyanide or azide in known manner into a compound of general formula I in which R^6 or R^7 is a halogen atom or a cyano or azido group or, in known manner, is deoxygenated to give a compound of general formula I, in which R^6 or R^7 is a hydrogen atom or a compound thus obtained of general formula I, in which R^6 or R^7 is an azido group, is reduced in known manner to a compound of general formula I in which R^6 or R^7 is an amino group and, if desired, a compound of

general formula I, in which Y is a hydrogen atom, is converted in known manner into a mono-, di- or tri-phosphate and, if desired, a free base or acid obtained is converted into an appropriate salt or a salt obtained
5 is converted into the corresponding free base or acid.

The compounds of general formula II are reacted with the compounds of general formula III especially advantageously under phase transfer conditions. Under the conditions of phase transfer catalysis, the bases
10 of general formula II are converted into a corresponding anion, for example by means of a 50% aqueous solution of sodium hydroxide. The anion thus obtained is hydrophobed by a phase transfer catalyst, for example tris-[2-(2-methoxyethoxy)-ethyl]-amine, and transported into the
15 organic phase in which it reacts with the reactive compound of general formula III.

As reactive groups Z in the compounds of general formula III, there are preferably used halogen atoms and alkoxy radicals. In the case of this reaction, the
20 hydroxyl groups of the sugar residue are protected in the usual way by conventional oxygen protective groups, for example toluoyl, benzoyl or acetyl radicals. After completion of the reaction, the oxygen protective groups can again be split off in known manner under alkaline
25 conditions, a 1M methanolic menthanolate solution preferably being used.

During the reaction, it can also be preferable to

keep the radicals R^1 , R^2 , R^3 and R^4 protected by appropriate protective groups.

Another advantageous method for the preparation of compounds of general formula IV is the solid-liquid
5 phase transfer process with the use of solid, powdered potassium hydroxide, the above-mentioned kryptand, as well as compounds of general formulae II and III in an aprotic solvent.

Compounds of general formula I, in which R^6 or R^7
10 is a halogen atom or an azido group, are preferably prepared by starting from a compound of general formula I, in which R^6 or R^7 is a hydroxyl group. The hydroxyl group in the 5'-position is first to be selectively protected. For this purpose, too, known processes are
15 available. For example, in nucleotide chemistry, the 4,4'-dimethoxy-triphenylmethyl radical has proved to be useful. After the reaction has taken place, this can again be easily split off by mild acid hydrolysis, whereas the also acid-labile glycosidic bond is not
20 hydrolysed under these conditions. The reaction of the nucleoside to be protected with the oxygen protective group reagent for the 5'-hydroxyl group is carried out in an appropriate organic solvent, preferably in dry pyridine, with a small excess of the oxygen protective
25 group reagent, as well as possibly of an appropriate adjuvant base, for example N-ethyldiisopropylamine. The so protected compound of general formula I is

reacted with a halide, preferably with an alkali metal halide or an organic halide, or with an azide, preferably with an alkali metal azide, in known manner. The hydroxyl group on the C-3' atom is thereby nucleophilically substituted by the halide or azide.

Compounds of general formula I, in which R^6 or R^7 is a hydroxyl group, can also, after previous protection of the 5'-hydroxyl group in the above-described manner, be desoxygenated by known methods to give compounds of general formula I, in which R^6 and R^7 are hydrogen atoms. For this purpose, the compound of general formula I, in which R^6 or R^7 is a hydroxyl group and in which the 5'-hydroxyl group has been protected in the above-described way and other functional radicals also carry protective groups, is first converted into a 3'-O-thiocarbonyl derivative which is subsequently reduced radically with tributyl tin hydride. Such methods for the desoxygenation of 2'-desoxynucleosides to give 2',3'-didesoxynucleosides are known, the Barton desoxygenation method having proved to be especially favourable (J. Chem. Soc., Perkin Trans. I (1975), 1574).

Compounds of general formula I, in which R^6 or R^7 is an amino group, are preferably prepared by reducing a compound of general formula I, in which the substituent R^6 or R^7 is an azido group. This reduction of the azido group to the amino group can be carried out by various generally known methods, the reduction with

hydrogen in the presence of a palladium-charcoal catalyst having proved to be especially advantageous.

The phosphate groups are introduced into compounds of general formula I, in which Y is a hydrogen atom, in known manner. The monophosphates are obtained, for example, by phosphorylating compounds of general formula I, in which Y is a hydrogen atom, with phosphorus oxychloride in trimethyl phosphate. The triethylammonium salts obtained in this way can be converted in known manner into other salts by transsalification. The di- and triphosphates are obtained according to known methods, preferably from the monophosphates, by reaction with orthophosphates or pyrophosphates. Their various salts can also be prepared by known methods.

Compounds of general formula II are either known or can be prepared analogously to known compounds. Such methods of preparation are described, for example, in Chemische Berichte, 110, 1462/1977; J. Chem. Soc., 1960, 131; and Tetrahedron Letters, 21, 3135/1980.

Some of the compounds of general formula III are also known. Compounds which have not hitherto been described can be prepared completely analogously to the known compounds. The preparation of such compounds is described, for example, in Chem. Ber., 93, 2777/1960 and in Synthesis, 1984, 961.

The new compounds according to the present invention possess valuable pharmacological properties.

In particular, by inhibition of the enzyme reverse transcriptase, the multiplication of retroviruses is prevented, i.e. the compounds according to the present invention possess especially cytostatic, as well as
5 antiviral properties.

The structural units of nucleic acids contain, as glycosidic components, either the β -D-ribofuranosyl radical or the 2-desoxy derivative thereof. Besides these aglyconic radicals, modified D-ribofuranosyl
10 derivatives are also found in nucleoside antibiotics. Thus, for example cordycepin, which can be isolated from culture filtrates of Cordyceps militaris, contains the monosaccharide cordycepose. Besides this 2'- or 3'-desoxy derivative of the ribonucleosides, some consider-
15 able time ago, 2',3'-didesoxynucleosides have been prepared synthetically. They have an anti-viral action and can, in particular, via the inhibition of the enzyme reverse transcriptase, inhibit the multiplication of retroviruses (cf. Proc. Natl. Acad. Sci. USA, 83, 1911/
20 1986 and Nature, 325, 773/1987). The inhibitory action on the HIV virus, the cause of AIDS, is of especial therapeutic interest. However, they have the disadvantage that they are also inhibitors of cellular DNA polymerase so that they act cytotoxically. Furthermore, they can
25 be deactivated by cellular enzymes. The compounds of general formula I do not display these disadvantages. They have an antiviral action without being cytotoxic.

The compounds of general formula I according to the present invention can also be advantageously used for DNA sequencing according to Sanger's method. The sequencing of d(G-C)-rich DNA fragments is, in particular, made difficult by the formation of secondary structures which lead to a band compression in the region of d(G-C) clusters. The reason for this is the Hoogsteen base pairing of guanosine molecules. By means of the replacement of 2'-desoxyguanosine triphosphate by the compounds according to the present invention, in which R^6 is a hydroxyl group, the band compression is largely overcome.

The compounds of general formula I according to the present invention, in which R^6 and R^7 are hydrogen atoms, are used in DNA sequencing by Sanger's method as chain terminators instead of the known 2',3'-dideoxy compounds.

Nucleic acids which, as structural components, contain one or more compounds of general formula I, can be prepared according to known processes (for example as described in Nucleic Acids Research, 14(5), 2319 et seq./1986). However, they also result, for example, in the case of the DNA sequencing. If compounds of general formula I, in which R^6 is a hydroxyl group, are used as structural components, then a nucleic acid can contain several such structural components; if, as structural component, a compound of general formula I is used, in which R^6 is a hydrogen atom, then such a structural component can only be incorporated once, namely, on the

end of the chain. The nucleic acids according to the present invention are made up of 2 to 1000 and preferably of 8 to 50 nucleotide structural components, nucleic acids with 15 to 30 nucleotide structural components
5 being especially preferred.

These nucleic acids can also be used as antiviral agents. As so-called anti-sense nucleic acids, these nucleic acids hybridise with the ssDNA/RNA of the virus and make difficult the transcription to the virus DNA.
10 Such nucleic acids can be used especially as agents against AIDS since they are not decomposed or only decomposed with difficulty by the cell's own restriction enzymes.

For the preparation of pharmaceutical compositions,
15 the compounds of general formula I, the pharmacologically compatible salts thereof or nucleic acids containing them are mixed in known manner with appropriate pharmaceutical carrier substances, aroma, flavouring and colouring materials and formed, for example, into tablets or
20 dragees or, with the addition of appropriate adjuvants, are suspended or dissolved in water or an oil, for example olive oil.

It will be understood that the salts of compounds (I), when used in pharmaceutical compositions will suitably be both pharmacologically compatible and pharmaceutically acceptable, by which is intended salts which have the required characteristics to render them suitable for formulation in pharmaceutical compositions for administration to living bodies.

10 The compounds according to the present invention can be administered enterally or parenterally in liquid or solid form. As injection medium it is preferred to use water which contains the additives usual in the case of injection solutions, such as stabilising agents,

solubilising agents and/or buffers.

Such additives include, for example, tartrate and citrate buffers, ethanol, complex formers (such as ethylenediamine-tetraacetic acid and the non-toxic salts thereof) and high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular weight fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycols). Compositions suitable for oral administration can, if desired, contain flavouring and sweetening agents.

The compounds according to the present invention are usually administered in an amount of from 1 to 100 mg. and preferably of from 2 to 80 mg. per day and per kg. body weight. It is preferred to divide up the daily dose into 2 to 5 administrations, in which case each administration comprises 1 or 2 tablets with a content of active material of from 5 to 1000mg. The tablets can also be retarded, in which case the number of administrations per day can be reduced to from 1 to 3. The active material content of the retarded tablets can be from 20 to 2000 mg. The active material can also be administered by injection one to eight times per day

or by continuous infusion, in which case amounts of from 500 to 4000 mg./day normally suffice.

The following Examples are given for the purpose of illustrating the present invention:-

5 Example 1.

2-Amino-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosyl-purin-6-one.

a) 2-[(4,4'-Dimethoxytriphenylmethyl)-amino]-7-desaza-2'-desoxy-5'-O-(4,4'-dimethoxytriphenylmethyl)-9- β -D-ribofuranosylpurin-6-one.

10 1.0 g. (3.8 mMole) 7-desaza-2'-desoxyguanosine is evaporated twice with dry pyridine and then suspended in 20 ml. pyridine. 4.0 g. (11.8 mMole) 4,4'-dimethoxy-triphenylmethyl chloride and 2.5 ml. (14.6 mMole) Hünig
15 base (N-ethyldiisopropylamine) are added thereto and the reaction mixture is stirred for 3 hours at ambient temperature.

The reaction mixture is subsequently introduced into 150 ml. of a 5% aqueous solution of sodium
20 bicarbonate and extracted twice with 150 ml. amounts of dichloromethane. The combined organic extracts are dried over anhydrous sodium sulphate, filtered and chromatographed on silica gel 60 H (column 10 x 4 cm., dichloromethane/acetone 9:1 v/v). After evaporation of the main
25 zone, the residue is dissolved in a little dichloromethane and added dropwise to a mixture of n-hexane/diethyl ether (1:1 v/v). After filtration, there are obtained 2.04 g.

(61% of theory) of the desired colourless, amorphous compound. TLC (silica gel, dichloromethane/acetone (8:2 v/v): $R_F = 0.7$; UV (methanol: $\lambda_{\max} = 272$, 283 nm (shoulder) ($\epsilon = 18800$, 16400).

- 5 $^1\text{H-NMR}$ ($[\text{D}_6]$ DMSO): $\delta = 1.75$ (m, 2'-H_b), 1.86 (m, 2'-H_a); 3.09 (m, 5'-H), 3.79 (m, 4'-H), 4.10 (m, 3'-H), 5.19 (d, 3'-OH, $J = 4.3$ Hz), 5.61 (pt, 1'-H, $J = 6.5$ Hz), 6.16 (d, 6-H, $J = 3.5$ Hz), 6.62 (d, 5-H, $J = 3.5$ Hz), 10.35 (s, NH).

- 10 Analysis for $\text{C}_{53}\text{H}_{50}\text{N}_4\text{O}_8$ (M.W. 871.0)
 calc.: C 73.07; H 5.79; N 6.43
 found: 73.02; 5.98; 6.34

- b) 2-[(4,4'-Dimethoxytriphenylmethyl)-amino]-7-desaza-2'-desoxy-3'-O-phenoxythiocarbonyl-5'-O-(4,4'-dimethoxy-triphenylmethyl)-9- β -D-ribofuranosylpurin-6-one.
- 15

- A suspension of 1.0 g. (1.1 mMole) of the compound of 1a) in 15 ml. dry acetonitrile is mixed with 300 mg. (2.5 mMole) *p*-dimethylaminopyridine and 300 μl . (2.2 mMole) phenoxythiocarbonyl chloride and stirred for 16
- 20 hours at ambient temperature. The reaction mixture is evaporated and the residue chromatographed on a silica gel 60 H column (column 10 x 4 cm., dichloromethane/acetone; 8:2 v/v). The residue obtained by evaporation of the main zone is dissolved in a little dichloromethane
- 25 and precipitated out by the dropwise addition of a mixture of *n*-hexane/diethyl ether (1:1 v/v) to give 0.99 g. (89% of theory) of a colourless, amorphous

substance. TLC (silica gel, methylene dichloride/acetone (8:2 v/v): $R_f = 0.8$; UV (methanol): $\lambda_{\max} = 269, 282 \text{ nm}$ (shoulder) ($\epsilon = 19300, 16000$).

$^1\text{H-NMR}$ ($[\text{D}_6]\text{DMSO}$): $\delta = 2.06$ (m, $2'\text{-H}_b$), 2.34 (m, $2'\text{-H}_a$),
 5 3.26 (m, $5'\text{-H}$), 4.25 (m, $4'\text{-H}$), 5.61 (m, $3'\text{-H}$ and $1'\text{-H}$),
 6.23 (d, 6-H , $J = 3.5 \text{ Hz}$), 6.67 (d, 5-H , $J = 3.5 \text{ Hz}$),
 10.41 (s, NH).

Analysis for $\text{C}_{60}\text{H}_{54}\text{N}_4\text{O}_9\text{S}$ (M.W. 1007.2)

calc. : C 71.77, H 5.40, N 5.56, S 3.18
 10 found: 71.26, 5.43, 5.52, 3.11

c) 2-[(4,4'-Dimethoxytriphenylmethyl)-amino]-7-desaza-2',3'-didesoxy-5'-O-(4,4'-dimethoxytriphenylmethyl)-9- β -D-ribofuranosylpurin-6-one.

500 mg. (0.5 mMole) of the compound of 1b) in 20 ml.
 15 freshly distilled toluene are mixed with 30 mg. (0.2 mMole) 2,2'-azo-bis-(2-methylpropionic acid nitrile) and 300 μl . (1.1 mMole) tributyl tin hydride and stirred for 3 hours under an atmosphere of argon at 80°C . (TLC monitoring, chloroform/methanol 97:3 v/v). After
 20 completion of the reaction, the reaction mixture is evaporated and the residue chromatographed on silica gel 60 H (column 30 x 4 cm.; dichloromethane/methanol 99:1 v/v). After evaporation of the main zone and taking up in a little dichloromethane, 320 mg. (75% of theory) of
 25 the desired amorphous, colourless compound is precipitated out by dropping into n -hexane/diethyl ether. TLC (silica gel, methylene chloride/methanol, 95:5 v/v):
 $R_f = 0.5$.

$^1\text{H-NMR}$ ($[\text{D}_6]\text{DMSO}$): δ = 1.63, 1.80 (2 m, 2'-H and 3'-H), 3.07 (m, 5'-H), 4.06 (m, 4'-H), 5.43 (m, 1'-H), 6.11 (d, 6-H, J = 3.5 Hz), 6.65 (d, 5-H, J = 3.5 Hz), 10.34 (s, NH).

- 5 d) 2-Amino-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosyl-purine-6-one.

300 mg. (0.35 mMole) of the compound from 1c) are dissolved in 10 ml. 80% acetic acid and stirred for 15 minutes at ambient temperature. Subsequently, the solvent is stripped off at oil pump vacuum and the residue evaporated several times with water. The crude product is chromatographed on silica gel 60H (column 10 x 4 cm., dichloromethane/methanol 9:1 v/v). The foamy substance obtained by evaporation of the main fraction is crystallised from a little methanol to give 50 mg. (57% of theory) of colourless needles; m.p. 228°C. (decomp.). TLC (silica gel, dichloromethane/methanol 9:1 v.v): R_F = 0.3. UV (methanol): λ_{max} = 261, 281 nm (shoulder) (ϵ = 13300, 7800).

$^1\text{H-NMR}$ ($[\text{D}_6]\text{DMSO}$): δ = 1.96 (m, 3'-H), 2.08, 2.27 (2 m, 2'-H_a and 2'-H_b), 3.48 (m, 5'-H), 3.97 (m, 4'-H), 4.86 (t, 5'-OH, J = 5.4 Hz), 6.12 (pt, 1'-H, J = 5.5 Hz), 6.24 (m, NH₂ and 6-H), 6.92 (d, 5-H, J = 3.5 Hz), 10.34 (s, NH).

Analysis for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_3$ (M.W. 250.3)

calc. :	C 52.79,	H 5.64,	N 22.39
found :	52.98,	5.80,	22.55

In an analogous manner, via the corresponding 2'-desoxynucleosides and subsequent deoxygenation as in c), there are obtained the following compounds:

A) 3,7-didesaza-2',3'-didesoxy-9-β-D-ribofuranosyl-

5 purine

UV (0.1 N HCl): $\lambda_{\max} = 224, 274 \text{ nm}$

Analysis for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$ (M.W. 218.2)

calc. : C 66.0, H 6.4, N 12.8

found : 66.1, 6.4, 12.6

10 B) 3,7-didesaza-2',3'-didesoxy-9-β-D-ribofuranosyl-
 purin-6-one

UV (methanol): $\lambda_{\max} = 264 \text{ nm}$ ($\epsilon = 11600$), 282 nm ($\epsilon = 8000$), 295 nm ($\epsilon = 5200$)

Analysis for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3$ (M.W. 234.2)

15 calc. : C 61.5, H 6.0, N 11.95

found : 61.3, 6.1, 11.8

C) 2-chloro-6-methoxy-3,7-didesaza-2',3'-didesoxy-9-β-
 D-ribofuranosylpurine

UV (methanol): $\lambda_{\max} = 271, 280 \text{ nm}$

20 Analysis for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_3\text{Cl}$ (M.W. 282.6)

calc. : C 55.2, H 5.3, N 9.9

found : 55.1, 5.3, 9.9

D) 6-amino-3,7-didesaza-2',3'-didesoxy-9-β-D-ribo-
 furanosylpurine

25 Analysis for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2$ (M.W. 233.2)

calc. : C 63.65, H 6.16 N 17.13

found : 63.62, 6.11, 17.01

UV (methanol) $\lambda_{\max} = 271 \text{ nm}$ ($\epsilon = 12800$)

E) 3,7-didesaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine-2,6-dione

Analysis for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4$ (M.W. 250.2)

5	calc. :	C 57.55	H 5.6	N 11.2
	found :	57.50	5.7	11.2

Example 2.

2-{[(Dimethylamino)-methylene]-amino}-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurin-6-one.

10 a) 2-[(Dimethylamino)-methylene]-amino-7-desaza-2'-desoxy-9- β -D-ribofuranosylpurin-6-one.

270 mg. (1.01 mMole) 7-desaza-2'-desoxyguanosine in 5 ml. dry, amine-free dimethylformamide are mixed with 2 ml. (11.7 mMole) N,N-dimethylformamide diethyl acetal
 15 and stirred for 1 hour at 50°C. under an atmosphere of argon. Subsequently, the reaction mixture is evaporated in a vacuum and the residue chromatographed on silica gel 60 H (column 10 x 4 cm., dichloromethane/methanol 9:1 v/v). By evaporation of the solvent, from the main
 20 zone there are obtained 230 mg. (71% of theory) of a pale yellow, amorphous substance. TLC (silica gel, dichloromethane/methanol 9:1 v/v): $R_f = 0.3$.

UV (methanol): $\lambda_{\max} = 240, 311 \text{ nm}$ ($\epsilon = 18300, 17400$).
 $^1\text{H-NMR}$ ($[\text{D}_6]$ DMSO: $\delta = 2.15$ (m, 2'- H_b), 2.41 (m, 2'- H_a),
 25 3.02, 3.15 (s, 2 CH_3), 3.52 (m, 5'-H), 3.79 (m, 4'-H), 4.32 (m, 3'-H), 4.91 (t, 5'-OH, $J = 5.4 \text{ Hz}$), 5.27 (d, 3'-OH, $J = 3.5 \text{ Hz}$), 6.34 (d, 6-H, $J = 3.5 \text{ Hz}$),

6.45 (pt, 1'-H, $J = 7.0$ Hz), 7.07 (d, 5-H, $J = 3.5$ Hz),
8.56 (s, NH=C), 11.04 (s, NH).

Analysis for $C_{14}H_{19}N_5O_4$ (M.W. 321.3)

calc. : C 52.33, H 5.96, N 21.79

5 found : 52.48, 6.14, 21.69

b) 2-([(Dimethylamino)-methylene]-amino)-7-desaza-2'-desoxy-5'-O-(4,4'-dimethoxytriphenylmethyl)-9- β -D-ribofuranosylpurin-6-one.

10 100 mg. (0.31 mMole) of the compound from 2a) are dissolved in 2 ml. dry pyridine, mixed with 170 mg. (0.5 mMole) 4,4'-dimethoxytriphenylmethyl chloride and 0.2 ml. (1.2 mMole) Hünig base and stirred for 3 hours at ambient temperature. Subsequently, the reaction mixture is evaporated and the residue chromatographed
15 on silica gel 60 H (column 10 x 2.5 cm., elution agent chloroform/methanol 99:1 v/v). The residue obtained by evaporation of the main fraction is dissolved in methylene chloride and, by dropping into a mixture of n-hexane/diethyl ether (1:1 v/v), 160 mg. (84% of
20 theory) of a colourless, amorphous substance are precipitated out. TLC (silica gel, methylene chloride/methanol 9:1 v/v): $R_F = 0.6$.

UV (methanol): $\lambda_{max} = 236, 311$ nm ($\epsilon = 38200, 18100$).

25 1H -NMR ($[D_6]$ DMSO): $\delta = 2.23$ (m, 2'-H_b), 2.42 (m, 2'-H_a), 3.03 (s, CH₃), 3.14 (m, 5'-H and CH₃), 3.90 (m, 4'-H), 4.33 (m, 3'-H), 5.34 (d, 3'-OH, $J = 4.3$ Hz), 6.34 (d, 6-H, $J = 3.5$ Hz), 6.49 (pt, 1'-H, $J = 6.8$ Hz), 6.90 (d,

5-H, $J = 3.5$ Hz), 8.58 (s, NH=C), 11.07 (s, NH).

Analysis for $C_{35}H_{37}N_5O_6$ (M.W. 623.7)

calc. : C 67.40, H 5.98, N 11.23

found : 67.31, 6.00, 11.17

- 5 c) 2-{[(Dimethylamino)-methylene]-amino}-7-desaza-2'-desoxy-3'-O-phenoxythiocarbonyl-5'-O-(4,4'-dimethoxytriphenylmethyl)-9- β -D-ribofuranosylpurin-6-one.

- 900 mg. (1.4 mMole) of the compound from 2b), dissolved in 15 ml. dry dichloromethane, are mixed with
10 340 mg. (2.8 mMole) p-dimethylaminopyridine and 250 μ l. (1.8 mMole) phenoxythiocarbonyl chloride and stirred for 16 hours at ambient temperature. The solution is evaporated in a vacuum and the residue chromatographed on
15 silica gel 60 H (column 20 x 4 cm., chloroform/acetone 7:3 v/v). The residue obtained by evaporation of the main zone is taken up in a little dichloromethane and the desired colourless, amorphous compound precipitated out by dropping into n-hexane/diethyl ether (1:1 v/v). TLC (silica gel, methylene chloride/methanol 95:5 v/v):
20 $R_F = 0.5$.
UV (methanol): $\lambda_{max} = 235, 277$ (shoulder), 283, 312 nm ($\epsilon = 41300, 11400, 12600, 17000$).
 1H -NMR ($[D_6]$ DMSO): $\delta = 2.73$ (m, 2'-H_b), 2.97 (m, 2'-H_a), 3.01, 3.10 (s, 2 CH₃), 3.37 (m, 5'-H), 4.33 (m, 4'-H),
25 5.90 (m, 3'-H), 6.40 (d, 6-H, $J = 3.5$ Hz), 6.55 (pt, 1'-H), 6.98 (d, 5-H, $J = 3.5$ Hz), 8.58 (s, CH=N), 11.30 (s, NH).

Analysis for $C_{42}H_{41}N_5O_7S$ (M.W. 759.9)

calc. : C 66.39, H 5.44, N 9.22, S 4.22

found : 66.49, 5.55, 9.25, 4.29

d) 2-{[(Dimethylamino)-methylene]-amino}-7-desaza-
5 2',3'-didesoxy-5'-O-(4,4'-dimethoxytriphenylmethyl)-
9- β -D-ribofuranosylpurin-6-one.

500 mg. (0.7 mMole) of the compound from 2c),
dissolved in 20 ml. freshly distilled toluene, are mixed
with 25 mg. (0.15 mMole) 2,2'-azo-bis-(2-methylpropionic
10 acid nitrile) and 500 μ l. (1.9 mMole) tributyl tin
hydride and stirred for 16 hours at 80°C. under an
atmosphere of argon. Subsequently, the reaction mixture
is evaporated under oil pump vacuum and the residue
chromatographed on silica gel 60 H (column 20 x 4 cm.,
15 dichloromethane/acetone 9:1 v/v, chloroform/acetone 7:3
v/v, chloroform/acetone 6:4 v/v). The residue obtained
by evaporation of the main fraction is dissolved in a
little dichloromethane and precipitated out by dropping
into n-hexane/diethyl ether to give 320 mg. (80% of
20 theory) of the desired colourless, amorphous compound.
TLC (silica gel, methylene chloride/methanol 95:5 v/v):
 R_f = 0.3.
UV (methanol): λ_{max} . = 236, 277 (shoulder), 284, 312 nm
(ϵ = 37200, 12000, 13500, 18000).
25 1H -NMR ($[D_6]$ DMSO): δ = 2.02 (m, 3'-H), 2.20, 2.33 (m,
2'-H_a and 2'-H_b), 3.02, 3.13 (s, 2 CH₃), 3.08 (m, 5'-H),
4.17 (m, 4'-H), 6.31 (d, 6-H, J = 3.5 Hz), 6.38 (m, 1'-H),

6.92 (d, 5-H, $J = 3.5$ Hz), 8.61 (s, CH=N), 11.03 (s, NH).

Analysis for $C_{35}H_{37}N_5O_7$ (M.W. 607.7)

calc. : C 69.18, H 6.14, N 11.52

found : 69.23, 6.24, 11.61

- 5 e) 2-{[(Dimethylamino)-methylene]-amino}-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurin-6-one.

130 mg. (0.21 mMole) of the compound from 2d) are dissolved in 80% acetic acid and stirred for 15 minutes at ambient temperature. Subsequently, the acetic acid is evaporated off under oil pump vacuum and the residue is chromatographed on silica gel 60 H (column 20 x 2 cm., dichloromethane/methanol 95:5 v/v). The residue obtained by evaporation of the main fraction is foamed up by repeated evaporation with acetone to give 43 mg. (67% of theory) of the desired colourless, amorphous compound. TLC (silica gel, dichloromethane/methanol 9:1 v/v): $R_f = 0.5$.

UV (methanol): $\lambda_{max.} = 239, 282$ (shoulder), 311 nm ($\epsilon = 17400, 10500, 16900$).

- 20 1H -NMR ($[D_6]$ DMSO): $\delta = 2.06, 2.32$ (m, 2'-H and 3'-H), 3.01, 3.14 (s, 2 CH_3O), 3.51 (m, 5'-H), 4.00 (m, 4'-H), 4.87 (t, 5'-OH), 6.33 (m, 1'-H and 6-H, $J = 3.3$ Hz), 7.05 (d, 5-H, $J = 3.3$ Hz), 8.59 (s, CH=N), 11.02 (s, NH).

Analysis for $C_{14}H_{19}N_5O_3$ (M.W.305.3)

25 calc. : C 55.07, H 6.27, N 22.94

found : 55.23, 6.41, 22.75

Example 3.

2-Amino-6-methoxy-7-desaza-2',3'-didesoxy-9-β-D-ribofuranosylpurine.

a) 2-Amino-6-methoxy-7-desaza-2'-desoxy-9-β-D-ribofuranosylpurine.

5 543 mg. (10 mMole) finely powdered potassium hydroxide and 68 mg. (0.2 mMole) tetrabutylammonium hydrogen sulphate in 30 ml. anhydrous dichloromethane are stirred for 15 minutes at ambient temperature under
10 an atmosphere of nitrogen. Subsequently, the reaction mixture is mixed with 330 mg. (2 mMole) 2-amino-6-methoxy-7-desazapurine (2-amino-4-methoxy-7H-pyrrolo[2,3-d]-pyrimidine) and stirred for a further 30 minutes. After the addition of 884 mg. (2.2 mMole) 2-desoxy-3,5-di-O-
15 p-toluoyl-β-D-erythro-pentofuranosyl chloride, stirring is continued for a further 3 minutes. Insoluble components are filtered off with suction, washed with a little dichloromethane and the filtrate concentrated to about 10 ml. After mixing with 3 ml. 1M sodium methoxide in
20 methanol, stirring is continued for 3 hours at ambient temperature. After neutralisation with acetic acid, the solvent is stripped off, the residue is taken up in hot water, filtered and the filtrate chromatographed on an exchanger column of Dowex* (1 x 2 OH form, 30 x 3 cm.)
25 (water/methanol 9:1 v/v). After stripping off the solvent and recrystallising from water, from the main zone there are obtained 260 mg. (63% of theory) of

* Trade Mark

colourless crystals; m.p. 152 - 154°C. TLC (silica gel, dichloromethane/methanol 9:1 v/v): $R_f = 0.7$.
 UV (methanol): $\lambda_{max.} = 225, 259, 285$ ($\epsilon = 24900, 3600, 7600$)

5 1H -NMR ($[D_6]$): $\delta = 6.27$ (1H, d, $J = 3.7$ Hz), 6.42 (1H, dd, $J_{1',2'a} = 8.4$ Hz, $J_{1',2'b} = 5.9$ Hz), 7.10 (1H, d, $J = 3.7$ Hz) ppm.

^{13}C -NMR ($[D_6]$ DMSO): $\delta = 52.49$ (OCH_3), 82.37 (C-1'), 98.85 (C-5), 119.45 (C-6) ppm.

10 b) The compound 2-amino-6-methoxy-7-desaza-2'-desoxy-9- β -D-ribofuranosylpurine obtained according to a) is desoxygenated in the manner described in Example 1c) to give 2-amino-6-methoxy-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine.

15 Example 4.

2-Amino-6-chloro-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine.

a) The compound is prepared, after acetylation of 2-amino-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurin-
 20 6-one (prepared according to Example 1d) by halogenation according to the method described in Liebigs Ann. Chem., 1987, 15 - 19.

b) The resulting crude mixture is, for the removal of the acetyl protective group, left to stand for 3 hours
 25 in methanolic ammonia solution at ambient temperature, then evaporated to dryness and finally chromatographed on silica gel with the elution agent chloroform/methanol.

After combining the main fractions and evaporating, the residue obtained is crystallised from water.
 UV (methanol): $\lambda_{\text{max.}}$ = 235, 258, 316 (ϵ = 27800, 4300, 5800).

- 5 Analysis for $\text{C}_{11}\text{H}_{13}\text{N}_4\text{O}_2\text{Cl}$ (M.W. 268.7)
 calc. : C 49.1, H 4.8, N 20.8, Cl 13.0
 found : 49.3, 4.85, 20.7, 13.1

Example 5.

- 10 2-Amino-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosyl-purine.
 268 mg. (1 mMole) 2-amino-6-chloro-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine are dissolved in 25 ml. 70% aqueous methanol, added to a suspension of 30 mg. prehydrogenated Pd/C (10%) in 25 ml. 70% aqueous
 15 methanol and hydrogenated until the take up of hydrogen is complete. The solvent is stripped off and the residue is crystallised from methanol. Yield 180 mg. (77% of theory).

- Analysis for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_2$ (M.W. 234.3)
 20 calc. : C 56.4, H 6.0, N 23.9
 found : 56.3, 6.0, 23.7
 UV (methanol): $\lambda_{\text{max.}}$ = 234, 256, 314 nm (ϵ = 30600, 4100, 5200).

Example 6.

- 25 2-Amino-6-mercapto-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine.
 536 mg. (2 mMole) 2-amino-6-chloro-7-desaza-2',3'-

didesoxy-9- β -D-ribofuranosylpurine and 1.5 g. (20 mMole) thiourea are suspended in 30 ml. ethanol and heated under reflux for about 15 hours. Thereafter, the solvent is distilled off, the residue is taken up in about 25 ml. methanol and then chromatographed on silica gel 60 H (column 20 x 3 cm., dichloromethane/methanol 9:1 v/v). By evaporation of the main fraction and crystallisation from methanol/water, there are obtained 230 mg. (43% of theory) of the thio compound.

10 Analysis for $C_{11}H_{14}N_4O_2S$ (M.W. 266.3)

calc. : C 49.6, H 5.3, N 21.0

found : 49.4, 5.4, 21.1

UV (methanol): $\lambda_{max.} = 235, 271, 345 \text{ nm}$ ($\epsilon = 176000, 11700, 18700$).

15 $^1\text{H-NMR}$ ($[D_6]\text{DMSO}$): $\delta = 1.9$ (m, 3'-H), 2.1 (m, 2'-H_b), 2.34 (m, 2'-H_a), 3.50 (m, 5'-H), 3.97 (m, 4'-H), 4.86 (t, 5'-OH), 6.12 (m, 1'-H), 6.24 (m, NH₂ and 8-H), 6.92 (d, 7-H), 11.1 (s, NH).

Example 7.

20 2,6-Diamino-7-desaza-2',3'-didesoxy-9- β -D-ribo-furanosylpurine.

268 mg. (1 mMole) 2-amino-6-chloro-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine are mixed with 40 ml. aqueous concentrated ammonia solution and heated for 60 hours at 65°C. on a waterbath in a tightly closed vessel. After evaporation of the solvent, the residue is chromatographed on a silica gel column, first with

dichloromethane/methanol (9:1 v/v) (starting material) and then with chloroform/methanol (4:1 v/v). After crystallisation from water, there are obtained 120 mg. (48% of theory) of the desired diamino compound.

5 Analysis for $C_{11}H_{15}N_5O_2$ (M.W. 249.3)

calc. : C 53.0, H 6.0, N 28.1

found : 53.15, 5.9, 28.2

UV (methanol): λ_{max} = 264, 284 nm (ϵ = 9800, 8000).

1H -NMR ($[D_6]$ DMSO: δ = 1.9 (m, 3'-H), 2.1, 2.4 (2 m, 2'-H_{a,b}), 3.4 (m, 5'-H), 3.8 (m, 4'-H), 4.8 (t, 5'-OH), 5.6 (s, NH_2), 6.2 (dd, 1'-H), 6.3 (d, 7-H), 6.7 (s, NH_2), 6.9 (d, 8-H).

Example 8.

2-Methylthio-6-methoxy-7-desaza-2',3'-didesoxy-9- β -

15 D-ribofuranosylpurine.

a) 2-Methylthio-6-methoxy-7-desaza-2'-desoxy-9- β -D-ribofuranosylpurine.

500 mg. (2.56 mMole) 4-Methoxy-2-methylthio-7H-pyrrolo[2,3-d]pyrimidine and 400 mg. (1.75 mMole) benzyltriethylammonium chloride are dissolved in 20 ml. dichloromethane with 20 ml. of a 5% aqueous solution of sodium hydroxide as counterphase and briefly mixed up in a vibratory mixer. 1.2 g. (3.1 mMole) 2-desoxy-3,5-di-O-(p-toluoyl)- β -D-erythro-pentofuranosyl chloride in a little dichloromethane, is added thereto and the vibratory mixing continued for 30 minutes. The organic phase is separated off and the aqueous phase shaken up

with dichloromethane. The combined organic extracts are washed with water and dried with anhydrous sodium sulphate. After filtration, the filtrate is evaporated and the residue dissolved in 100 ml. 1M sodium

- 5 methanolate in methanol. The solution is stirred for about 12 hours at ambient temperature, then evaporated and the residue is taken up in water and adsorbed on a Dowex 1-X2 ion exchanger column (30 x 3 cm., OH⁻ form). Elution with water-methanol (1:1 v/v) gives a main zone.
- 10 After evaporation of the solvent, the residue is re-crystallised from water; yield 321 mg. (40% of theory) of colourless needles; m.p. 118°C. TLC (silica gel; dichloromethane/acetone 8:2 v/v): $R_F = 0.26$.
 UV (methanol): $\lambda_{max.} = 283, 236 \text{ nm}$ ($\epsilon = 13000, 15500$).
 15 ¹H-NMR ([D₆]DMSO): $\delta = 2.20$ (m, 2'-H), 2.40 (m, 2'-H), 2.56 (s, CH₃S), 3.50 (m, 5'-H₂), 3.81 (m, 4'-H), 4.01 (s, CH₃O), 4.35 (m, 3'-H), 4.90 (t, 5'-OH, J = 5 Hz), 5.29 (d, 3'-OH, J = 4 Hz), 6.48 (d, 5-H, J = 4 Hz), 6.55 (t, 1'-H, J = 5 Hz), 7.47 (d, 6-H, J = 4 Hz).
- 20 Analysis for C₁₃H₁₇N₃O₄S (M.W. 311.4)
 calc. : C 50.15, H 5.50, N 13.50, S 10.30
 found : 50.28, 5.47, 13.56, 10.31
- b) 2-Methylthio-6-methoxy-7-desaza-2',3'-didesoxy-9-
 β -D-ribofuranosylpurine.

- 25 This is prepared by deoxygenation of the 2'-desoxy compound obtained according to a) in the manner described in Example 1c).

UV (methanol): $\lambda_{\text{max.}} = 283, 236$ ($\epsilon = 1300, 15500$)

Analysis for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$ (M.W. 295.4)

calc. : C 52.8, H 5.75, N 14.2

found : 52.6, 5.70, 14.2

5 Example 9.

6-Methoxy-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosyl-purine.

a) 6-Methoxy-7-desaza-2'-desoxy-9- β -D-ribofuranosyl-purine.

10 The synthesis of this compound takes place in the manner described in Liebigs Ann. Chem., 1985, 1360-1366.

b) The didesoxy derivative can be obtained by deoxygenation of the compound obtained in a) in the manner described in Example 1c).

15 An alternative way is the desulphurisation of 2-methylthio-6-methoxy-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine from Example 8, also in the manner described in Liebigs Ann. Chem., 1985, 1360 - 1366.

TLC (dichloromethane/methanol 9:1 v/v): $R_f = 0.8$.

20 UV (methanol): $\lambda_{\text{max.}} = 261$ nm ($\log(\epsilon) = 3.86$).

$^1\text{H-NMR}$ (DMSO-d_6): $\delta = 2.04$ (m, 3'-H), 2.24 (m, 2'-H_b), 2.40 (m, 2'-H_a), 3.55 (m, 5'-H), 4.04 (s, OCH_3), 4.07 (m, 4'-H), 4.93 (t, $J = 5.5$ Hz, 5'-OH), 6.47 (dd, $J = 4.4$ and 6.8 Hz, 1'-H), 6.55 (d, $J = 3.7$ Hz, 5-H),

25 7.66 (d, $J = 3.7$ Hz, 6-H), 8.42 (s, 2-H).

Analysis for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_3$ (M.W. 249.3)

calc. : C 57.8, H 6.0, N 16.8

found : 57.8, 6.05, 16.65

Another possibility for the preparation of this compound is described in Example 24i).

Example 10.

7-Desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurin-6-one.

5 The preparation of this compound takes place via the 2'-desoxy compound as described in Liebigs Ann. Chem., 1985, 312-320 and subsequent deoxygenation as described in Example 1c).

UV (methanol): $\lambda_{\text{max.}}$ = 258, 280 (shoulder) (ϵ = 9200, 10 6400).

TLC (dichloromethane/methanol 9:1 v/v): R_f = 0.5.

$^1\text{H-NMR}$ (DMSO- d_6): δ = 2.00 (m, 3'-H), 2.16 (m, 2'-H_b), 2.37 (m, 2'-H_a), 3.49 (dd, J = 4.9 and 11.6 Hz, 5'-H), 3.58 (dd, J = 4.2 and 11.6 Hz, 5'-H), 4.05 (m, 4'-H), 15 6.33 (dd, J = 4.2 and 6.9 Hz, 1'-H), 6.50 (d, J = 3.5 Hz, 5-H), 7.36 (d, J = 3.5 Hz, 6-H), 7.90 (s, 2H).

Analysis for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3$ (M.W. 235.2)

calc. : C 56.1, H 5.5, N 17.8

found : 56.0, 5.3, 18.0

20 A further possibility for the preparation of this compound is described in Example 24j).

Example 11.

7-Desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine-2,6-dione.

25 The synthesis of this compound takes place via the 2'-desoxy compound as described in Liebigs Ann. Chem., 1985, 312-320 and subsequent deoxygenation as described in Example 1c).

UV (phosphate buffer; pH 7.0): $\lambda_{\text{max.}} = 251, 280 \text{ nm}$
 ($\epsilon = 10500, 7400$)

Analysis for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_4$ (M.W. 251.4)

calc. : C 52.5, H 5.2, N 16.7

5 found : 52.3, 5.1, 16.5

Example 12.

2,6-Dimethoxy-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine.

This derivative is synthesised by phase transfer
 10 glycosylation and subsequent deoxygenation as described
 in Example 1c).

UV (methanol): $\lambda_{\text{max.}} = 257, 271 \text{ nm}$ ($\epsilon = 7300, 7400$)

Analysis for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_4$ (M.W. 279.3)

calc. : C 55.85, H 6.1, N 15.0

15 found : 55.7, 6.1 15.1

Example 13.

6-Amino-7-desaza-2',3'-didesoxy-9- β -D-ribofuranosyl-
 purin-2-one.

This compound is obtained according to J. Chem.
 20 Soc., Perkin Trans. II, 1986, 525 - 530 by phase transfer
 glycosylation of 2-methoxy-6-amino-7-desazapurine,
 subsequent demethylation and finally deoxygenation
 analogously to Example 1c).

UV (methanol): $\lambda_{\text{max.}} = 255, 305 \text{ nm}$ ($\epsilon = 7600, 7200$)

25 Analysis for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_3$ (M.W. 250.2)

calc. : C 52.7, H 5.6, N 22.4

found : 52.75, 5.5, 22.3

Example 14.

2-Amino-7-desaza-7-methyl-2',3'-didesoxy-9-β-D-ribofuranosylpurin-6-one.

This compound is synthesised via the 2'-desoxy-
5 nucleoside described in Liebigs Ann. Chem., 1984, 708-721 with subsequent deoxygenation as described in Example 1c).

UV (methanol): $\lambda_{\text{max.}}$ = 224, 264, 285 nm (shoulder)
(ϵ = 22500, 10500, 6500)

10 Analysis for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_3$ (M.W. 264.3)

calc. : C 54.5, H 6.05, N 21.2

found : 54.3, 6.1, 21.1

Example 15.

2-Amino-7-desaza-2',3'-didesoxy-3'-azido-9-β-D-

15 ribofuranosylpurin-6-one.

This compound is prepared by glycosylation of 2-amino-7-desazapurin-6-one with the azido sugar prepared according to Byatkina/Azhayev (Synthesis, 1984, 961-963).

UV (methanol): $\lambda_{\text{max.}}$ = 261, 281 nm (shoulder)
20 (ϵ = 13300, 7800).

Analysis for $\text{C}_{11}\text{H}_{13}\text{N}_7\text{O}_3$ (M.W. 291.3)

calc. : C 45.3, H 4.45, N 33.65

found : 45.4, 4.3, 33.4

Example 16.

25 3,7-Didesaza-2',3'-didesoxy-3'-azido-9-β-D-ribofuranosylpurine.

This compound is prepared by ribosidation of 3,7-

didesazapurine with the azido sugar prepared according to Byatkina/Azhayev (Synthesis, 1984, 961-963).

UV (methanol): $\lambda_{\text{max.}}$ = 224, 274 nm.

Analysis for $\text{C}_{12}\text{H}_{13}\text{N}_5\text{O}_2$ (M.W. 259.2)

5	calc. :	C 55.55,	H 5.0,	N 27.0
	found :	55.4,	5.1,	26.8

Example 17.

6-Amino-8-aza-7-desaza-2',3'-didesoxy-9- β -D-ribo-furanosylpurine (4-amino-1-(2-desoxy- β -D-erythro-pentofuranosyl)-1H-pyrazolo[3,4-d]pyrimidine)
 10 a) 4-Benzoylamino-1-(2'-desoxy-9- β -D-erythro-pentofuranosyl-5'-O-(4,4'-dimethoxytriphenylmethyl)-1H-pyrazolo[3,4-d]pyrimidine.

6-Amino-8-aza-7-desaza-2'-desoxy- β -D-ribo-furanosylpurine is prepared in the manner described in
 15 Helv. Chim. Acta, 68, 563 - 570/1985. The benzylation of the 4-amino group and the subsequent introduction of the dimethoxytrityl protective group is carried out analogously to known methods.

20 b) 4-Benzoylamino-1-(2'-desoxy- β -D-erythro-pentofuranosyl)-5'-O-(4,4'-dimethoxytriphenylmethyl)-3'-O-phenoxythiocarbonyl-1H-pyrazolo[3,4-d]pyrimidine.

200 mg. (0.3 mMole) of the product of Example 17a)
 25 are reacted in 4 ml. acetonitrile with 82 μ l. (0.6 mMole) phenyl chlorothiocarbonate at ambient temperature for 16 hours in the presence of 90 mg. (0.75 mMole) 4-

(dimethylamino)-pyridine. After chromatographic purification (silica gel, dichloromethane/ethyl acetate 95:5 v/v), there are isolated 150 mg. (63% of theory) of the desired product.

- 5 TLC (silica gel, dichloromethane/ethyl acetate, 95:5 v/v: $R_f = 0.4$.

$^1\text{H-NMR}$ ($[\text{D}_6]$ DMSO): $\delta = 3.26$ (m, 5'-H), 3.69 (s, 2 x OCH_3), 4.45 (m, 4'-H), 5.98 (m, 3'-H), 8.45 (s, 3-H), 8.78 (s, 6-H), 11.72 (s, NH).

- 10 c) 4-Benzoylamino-1-(2',3'-didesoxy-9- β -D-glycero-pentofuranosyl)-5'-O-(4,4'-dimethoxytriphenylmethyl)-1H-pyrazolo[3,4-d]pyrimidine.

200 mg. (0.25 mMole) of the product of Example 17b) are deoxygenated according to Barton's method in 7 ml. toluene with 150 μl . (0.55 mMole) tri-N-butyl stannane at 80°C. under an atmosphere of argon. After chromatography (silica gel, dichloromethane/ethyl acetate 95:5 v/v), there are obtained 120 mg. (75% of theory) of the desired colourless and amorphous product.

- 20 TLC (silica gel, dichloromethane/ethyl acetate 95:5 v/v): $R_f = 0.3$

$^1\text{H-NMR}$ ($[\text{D}_6]$ DMSO): $\delta = 2.16$ (m, 3'-H), 2.49 (m, 2'-H), 2.99 (m, 5'-H), 3.65, 3.68 (2s, 2 x OCH_3), 4.32 (m, 4'-H), 6.69 (m, 1'-H), 8.41 (s, 3-H), 8.80 (s, 6-H), 11.66 (s, NH).

- 25 d) 6-Amino-8-aza-7-desaza-2',3'-didesoxy-9- β -D-ribo-furanosylpurine (4-amino-1-(2',3'-didesoxy- β -D-glyceropentofuranosyl)-1H-pyrazolo[3,4-d]pyrimidine)

- a) 300 mg. (0.47 mMole) of the product of Example 17c) are treated in 40 ml. ammonia-saturated methanol at 60°C. for 4 hours and then evaporated to dryness. There are obtained 200 mg. (81% of theory) 4-amino-1-(2',3'-dideoxy- β -D-glyceropentofuranosyl)-5'-O-(4,4'-dimethoxy-triphenylmethyl)-1H-pyrazolo[3,4-d]pyrimidine in the form of a colourless foam after chromatography on silica gel (dichloromethane/acetone 7:3 v/v). TLC (silica gel, dichloromethane/acetone 8:2 v/v):
- 10 $R_f = 0.25$.
 $^1\text{H-NMR}$ ($[\text{D}_6]$ DMSO): $\delta = 2.16$ (m, 3'-H), 2.45 (m, 2'-H), 2.99 (m, 5'-H), 3.69, 3.70 (2s, 2 x OCH_3), 4.25 (m, 4'-H), 6.52 (m, 1'-H), 7.74 (s, NH_2), 8.06 (s, 3-H), 8.24 (s, 6-H).
- 15 b) 110 mg. (0.2 mMole) of the above product are stirred for 20 minutes at ambient temperature in 10 ml. 80% acetic acid. After chromatography (silica gel, dichloromethane/methanol 9:1 v/v), there is obtained the desired product in crystalline form. Subsequent re-
- 20 crystallisation from isopropanol/cyclohexane gives 40 mg. (85% of theory) of the desired product as a colourless solid.
- UV (methanol): $\lambda_{\text{max.}} = 260, 275 \text{ nm}$ ($\epsilon = 9000, 10200$).
- Analysis for $\text{C}_{10}\text{H}_{13}\text{H}_5\text{O}_2$ (M.W. 235.25)
- 25 calc. : C 51.06, H 5.57, N 29.77
 found : 50.96, 5.65, 29.80

^{13}C -NMR ($[\text{D}_6]$ DMSO): δ = 133 (C-8), 100.3 (C-5), 158.1 (C-6), 156.1 (C-2), 153.6 (C-4), 84.4 (C-1'), 30.4 (C-2'), 27.4 (C-3'), 81.7 (C-4'), 64.3 (C-5').

TLC (silica gel, dichloromethane/methanol 9:1 v/v):

5 R_f = 0.4.

UV (methanol): $\lambda_{\text{max.}}$ = 260, 275 nm (ϵ = 9000, 10200).

^1H -NMR ($[\text{D}_6]$ DMSO): δ = 2.11 (m, 3'-H), 2.40 (m, 2'-H), 3.36 (m, 1'-H), 4.08 (m, 4'-H), 4.75 (m, 5'-OH), 6.45 (m, 1'-H), 7.75 (s, NH_2), 8.14 (s, 3-H), 8.18 (s, 6-H).

10 Example 18.

a) 4,6-Dichloro-1-(2'-desoxy-3',5'-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-1H-pyrrolo[3,2-c]pyridine.

A solution of 300 mg. (1.6 mMole) 4,6-dichloro-1H-pyrrolo[3,2-c]pyridine in 75 ml. dry acetonitrile, which
 15 contains 450 mg. (8.0 mMole) potassium hydroxide and 30 mg. (0.1 mMole) tris-[2-(2-methoxyethoxy)-ethyl]-amine, is stirred at ambient temperature for 30 minutes under an atmosphere of nitrogen. While stirring, 625 mg. (1.6 mMole) α -chloro-2-desoxy-3,5-di-O-p-toluoyl-D-
 20 erythro-pentofuranose are added thereto and stirring continued for 15 minutes. Insoluble material is then filtered off and the filtrate is evaporated in a vacuum. The oily residue is chromatographed on silica gel (column 17 x 4 cm., elution agent dichloromethane/ethyl
 25 acetate 97:3 v/v). There are obtained 762 mg. (90% of theory) of the colourless, amorphous product.

^1H -NMR ($\text{Me}_2\text{SO}-d_6$): δ = 2.37 and 2.41 (2s, 2 CH_3), 2.77

(m, H-2's), 2.94 (m, H-2'), 4.57 (m, H-4', H-5'), 5.68 (m, H-3'), 6.66 (pt, H-1'), 6.71 (d, $J = 3.5$ Hz, H-3), 8.00 (s, H-7).

^{13}C -NMR ($\text{Me}_2\text{SO}-d_6$): $\delta = 36.8$ (C-2'), 64.2 (C-5'), 74.9 (C-3'), 81.7 (C-1'), 85.6 (C-4'), 102.0 (C-3), 106.1 (C-7), 123.1 (C-3a), 129.7 (C-2), 140.0 (C-6), 140.6 (C-4), 142.4 (C-7a).

b) 4,6-Dichloro-1-(2'-desoxy- β -D-erythro-pentofuranosyl)-1H-pyrrolo[3,2-c]pyridine.

10 500 mg. (0.93 mMole) of the compound of Example 18a) are dissolved in 30 ml. methanolic ammonia and stirred for 12 hours at 50°C . The solution is evaporated to dryness, the solid residue is adsorbed in silica gel 60 H (2 g.) and applied to a silica gel column (14 x 4 cm.,
15 elution agent chloroform/methanol 9:1 v/v). From the main fraction there is isolated the desired product in the form of a colourless oil which crystallises from aqueous ethanol in the form of colourless needles.

Yield 101 mg. (72% of theory); m.p. 180°C .

20 ^1H -NMR ($\text{Me}_2\text{SO}-d_6$): $\delta = 2.28$ (m, H-2's), 2.43 (m, H-2'a), 3.56 (m, H-5'), 3.85 (m, H-4'), 4.38 (m, H-3'), 5.02 (t, $J = 5.2$ Hz, 5'-OH), 5.34 (d, $J = 4.1$ Hz, 3'-OH), 6.42 (pt, H-1'), 6.67 (d, $J = 3.4$ Hz, H-3), 7.89 (d, $J = 3.4$ Hz, H-2), 7.96 (s, H-7).

25 ^{13}C -NMR ($\text{Me}_2\text{SO}-d_6$): $\delta = 40.6$ (C-2'), 61.5 (C-5'), 70.5 (C-3'), 85.5 (C-1'), 87.6 (C-4'), 101.3 (C-3), 106.1 (C-7), 123.1 (C-3a), 129.7 (C-2), 139.7 (C-6), 140.4 (C-4), 142.0 (C-7a).

c) 4-Amino-6-chloro-1-(2'-desoxy- β -D-erythro-pentofuranosyl)-1H-pyrrolo[3,2-c]pyridine.

460 mg. (1.52 mMole) of the compound of Example 18b) are dissolved in 6 ml. dry hydrazine and heated to 80°C. for 60 minutes. The hydrazine is removed under a vacuum and the oily residue evaporated twice with, in each case, 10 ml. ethanol. The residue is dissolved in 40 ml. aqueous ethanol and then 2 g. Raney nickel are added thereto and the mixture heated to the boil for 2 hours, while stirring. The catalyst is filtered off and thoroughly washed with hot aqueous ethanol. The filtrate is evaporated to dryness, the residue is dissolved in methanol, adsorbed on 2 g. silica gel and the solvent removed under a vacuum. This silica gel is suspended in chloroform/methanol (9:1 v/v) and applied to a silica gel column (6 x 3 cm.). Elution with chloroform/methanol (9:1 v/v) gives a colourless syrup from which, by crystallisation from methanol, the product can be obtained in the form of small, colourless crystals; m.p. 232°C. Yield: 207 g. (48% of theory).
TLC (chloroform/methanol 9:1 v/v): $R_F = 0.2$.
UV (methanol): $\lambda_{max.} = 277 \text{ nm}$ ($\epsilon = 14800$), 285 nm ($\epsilon = 13800$).
 $^1\text{H-NMR}$ ($\text{Me}_2\text{SO-d}_6$): $\delta = 2.20$ (m, H-2'm), 2.40 (m, H-2'a), 3.51 (m, H-5'), 3.78 (m, H-4'), 4.32 (m, H-3'), 4.89 (t, $J = 5 \text{ Hz}$, 5'-OH), 5.26 (d, $J = 4 \text{ Hz}$, 3'-OH), 6.19 (pt, H-1'), 6.55 (s, NH_2), 6.64 (d, $J = 3 \text{ Hz}$, H-3), 6.83 (s, H-7), 7.36 (d, $J = 3 \text{ Hz}$, H-2).

^{13}C -NMR ($\text{Me}_2\text{SO}-d_6$): δ = 40 (C-2'), 61.8 (C-5'), 70.6 (C-3'), 84.7 (C-1'), 87.2 (C-4'), 95.1 (C-7), 101.6 (C-3), 109.6 (C-3a), 123.5 (C-2), 141.0 (C-6), 141.4 (C-7a), 152.9 (C-4).

5 Analysis for $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{O}_3$

calc. : C 50.80, H 4.97, N 14.81, Cl 12.50
found : 50.91, 5.05, 14.75, 12.53

d) 4-Amino-1-(2'-desoxy- β -D-erythro-pentofuranosyl)-1H-pyrrolo[3,2-c]pyridine.

- 10 A solution of 200 mg. (0.7 mMole) of the compound from Example 18c) in 30 ml. methanol, which contains 0.4 ml. of ammonia-saturated methanol, is hydrogenated in the presence of palladium/charcoal (50 mg., 10% Pd) at ambient temperature for 30 hours. The catalyst is
- 15 filtered off and the solvent removed in a vacuum. Purification by flash chromatography (column 4 x 4 cm., elution agent chloroform/methanol/triethylamine 7:3:2 v/v/v) and crystallisation from methanol gives 70 mg. (40% of theory) of the desired product in the form of
- 20 colourless crystals; m.p. 205°C.

TLC (elution agent chloroform/methanol/triethylamine 7:3:2 v/v/v): R_f = 0.4.

UV (methanol): $\lambda_{\text{max.}}$ = 271 nm (ϵ = 12800).

- 25 ^1H -NMR ($\text{Me}_2\text{SO}-d_6$): δ = 2.20 (m, H-2'b), 2.42 (m, H-2'a), 3.51 (m, H-5'), 3.80 (m, H-4'), 4.32 (m, H-3'), 4.91 (m, 5'-OH), 5.32 (m, 3'-OH), 6.08 (s, NH_2), 6.23 (pt, H-1'), 6.65 (d, J = 3 Hz, H-3), 6.75 (d, J = 6 Hz, H-7),

7.35 (d, J = 3 Hz, H-2), 7.55 (d, J = 6 Hz, H-6).

$^{13}\text{C-NMR}$ ($\text{Me}_2\text{SO-d}_6$): δ = 39.8 (C-2'), 62.0 (C-5'), 70.8 (C-3'), 84.5 (C-1'), 87.1 (C-4'), 96.9 (C-7), 101.5 (C-3), 110.7 (C-3a), 122.5 (C-2), 139.7 (C-6), 140.0 (C-7a), 153.7 (C-4).

Analysis for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_3$

calc. : C 57.82, H 6.07, N 16.86

found : 57.97, 6.12, 16.74

Example 19.

10 a) 6-Chloro-1-(2'-desoxy- β -D-erythro-pentofuranosyl)-1H-pyrrolo[3,2-c]pyridin-4-one.

A solution of 400 mg. (1.32 mMole) of the compound of Example 18b) is heated to the boil for 30 hours in 2N aqueous sodium hydroxide solution with a small amount of 1,4-dioxan. The reaction mixture is neutralised with 2N hydrochloric acid, filtered and then applied to an Amberlite*XAD 4 column (17 x 2 cm.). Inorganic salts are removed by washing with water and then the product is eluted with methanol. Crystallisation from water gives 158 mg. (42% of theory) of colourless crystals; m.p. 242 - 243°C.

TLC (chloroform/methanol 8:2 v/v): R_f = 0.5.

UV (methanol): $\lambda_{\text{max.}}$ = 270 nm (ϵ = 11100), 292 nm (ϵ = 9300).

25 $^1\text{H-NMR}$ ($\text{Me}_2\text{SO-d}_6$): δ = 2.22 (m, H-2'b), 2.38 (m, H-2'a), 3.53 (m, H-5'), 3.80 (m, H-4'), 4.33 (m, H-3'), 4.96 (m, 5'-OH), 5.29 (m, 3'-OH), 6.22 (pt, H-1'), 6.54 (d,

* Trade Mark

-43-

$J = 3.3$ Hz, H-3), 6.96 (s, H-7), 7.38 (d, $J = 3.3$ Hz, H-2), 11.81 (br. NH).

^{13}C -NMR ($\text{Me}_2\text{SO}-d_6$): $\delta = 40.5$ (C-2'), 61.7 (C-5'), 70.6 (C-3'), 85.0 (C-1'), 87.4 (C-4'), 94.9 (C-7),
 5 104.1 (C-3), 114.0 (C-3a), 123.2 (C-2), 129.1 (C-6), 139.2 (C-7a), 158.7 (C-4).

Analysis for $\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}_4$

calc. : C 50.63, H 4.60, N 9.84, Cl 12.45

found : 50.79, 4.74, 9.80, 12.69

10 b) 1-(2'-Desoxy- β -D-erythro-pentofuranosyl)-1H-pyrrolo[3,2-c]pyridin-4-one.

A solution of 100 mg. (0.35 mMole) of the compound of Example 19a) in 15 ml. methanol is mixed with 0.5 ml. 25% aqueous ammonia solution and hydrogenated in the
 15 presence of palladium/animal charcoal (10% Pd, 15 mg.) for 3 hours at ambient temperature. The catalyst is filtered off and the filtrate evaporated to dryness. The solid residue is crystallised from water. There are obtained 51 mg. (58% of theory) of the desired product;
 20 m.p. 147 - 148°C.

TLC (elution agent chloroform/methanol 8:2 v/v):

$R_f = 0.3$.

UV (methanol): $\lambda_{\text{max.}} = 264$ nm ($\epsilon = 11700$), 282 nm (sh, $\epsilon = 8000$), 295 nm (sh, $\epsilon = 5100$).

25 ^1H -NMR ($\text{Me}_2\text{SO}-d_6$): $\delta = 2.22$ (m, H-2's), 2.40 (m, H-2's), 3.52 (m, H-5'), 3.81 (m, H-4'), 4.32 (m, H-3'), 4.93 (t, $J = 5.4$ Hz, 5'-OH), 5.32 (d, $J = 4.3$ Hz, 3'-OH),

6.21 (pt, H-1'), 6.54 (d, J = 3 Hz, H-3), 6.62 (d, J = 7 Hz, H-7), 7.03 (d, J = 7 Hz, H-6), 7.34 (d, J = 3 Hz, H-2), 10.87 (br NH).

^{13}C -NMR ($\text{Me}_2\text{SO}-d_6$): δ = 40 (C-2', superimposed by solvent signals), 61.8 (C-5'), 70.7 (C-3'), 84.8 (C-1'), 87.4 (C-4'), 93.8 (C-7), 104.6 (C-3), 115.9 (C-3a), 122.0 (C-2), 127.8 (C-6), 139.0 (C-7a), 159.6 (C-4).

Analysis for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4$

	calc. :	C 59.08,	H 6.10,	N 10.60
10	found :	59.09,	6.07,	10.65

Example 20.

a) 1-(2'-Desoxy- β -D-erythro-pentofuranosyl)-4,6-dichloro-5'-O-(4,4'-dimethoxytrityl)-1H-pyrrolo-[3,2-c]pyridine.

15 500 mg. (1.65 mMole) of the compound of Example 18b) are evaporated to dryness with 10 ml. pyridine. The material is dissolved in 10 ml. dry pyridine and 0.7 ml. (4.1 mMole) of Hünig's bases, as well as 690 mg. (2.0 mMole) 4,4'-dimethoxytrityl chloride, added

20 thereto. The solution is stirred for 1 hour at ambient temperature. After the addition of 75 ml. of 5% aqueous sodium bicarbonate solution, it is extracted twice with, in each case, 75 ml. dichloromethane. The combined

25 organic phases are dried over anhydrous sodium sulphate. The sodium sulphate is filtered off and the filtrate evaporated. The residue is applied to a silica gel column (30 x 3 cm.; elution agent dichloromethane/

acetone 99:1 v/v). The product is obtained from the main fraction in the form of a yellowish amorphous mass. The product is dissolved in diethyl ether and precipitated out with n-hexane. Yield 740 mg. (74% of theory).

5 $^1\text{H-NMR}$ ($\text{Me}_2\text{SO-d}_6$): δ = 2.39 (m, H-2'b), 2.64 (m, H-2'a), 3.09 (m, H-5'), 3.72 (s, 2 OCH_3), 3.96 (m, H-4'), 4.42 (m, H-3'), 5.41 (d, J = 4.8 Hz, 3'-OH), 6.47 (pt, H-1'), 6.65 (d, J = 3.5 Hz, H-3), 6.76 - 7.27 (aromat. H), 7.76 (d, J = 3.5 Hz, H-2), 7.89 (s, H-7).

10 $^{13}\text{C-NMR}$ ($\text{Me}_2\text{SO-d}_6$): δ = 40 (C-2' superimposed by solvent signals), 55.1 (2 OCH_3), 63.6 (C-5'), 70.05 (C-3'), 85.0 85.5. 85.5 (C-1', C-4', OCDMT), 101.3 (C-3), 106.2 (C-7), 123.2 (C-3a), 129.1 (C-2), 139.8 (C-6), 140.5 (C-4), 142.3 (C-7a).

15 Analysis for $\text{C}_{33}\text{H}_{30}\text{Cl}_2\text{N}_2\text{O}_5$

calc. : C 65.46, H 4.99, Cl 11.71, N 4.63

found : 65.47, 5.09, 11.78, 4.56

b) 1-(2'-Desoxy- β -D-erythro-pentofuranosyl)-4,6-dichloro-5'-O-(4,4'-dimethoxytrityl)-3'-O-phenoxy-
20 thiocarbonyl-1H-pyrrolo[3,2-c]pyridine.

300 mg. (0.5 mMole) of the compound of Example 20a) are dissolved in 11 ml. dry acetonitrile and 350 mg. (2.8 mMole) 4-dimethylaminopyridine and 150 μl . (1.1 mMole) phenyl chlorothiocarbonate added thereto and the
25 solution is stirred for 16 hours at ambient temperature. The reaction mixture is subsequently evaporated to dryness in a vacuum. The residue is chromatographed on

silica gel (elution agent dichloromethane). The colourless product is isolated from the main fraction. Yield 310 mg. (84% of theory).

$^1\text{H-NMR}$ ($\text{Me}_2\text{SO-d}_6$): δ = 2.92 (m, H-2'a,b), 3.35 (m, H-5'),
 5 3.72 (s, 2 OCH_3), 4.43 (m, H-4'), 5.89 (m, H-3'), 6.61
 (pt, H-1'), 6.71 (d, J = 3.5 Hz, H-3), 6.81 - 7.52
 (aromat. H), 7.76 (d, J = 3.5 Hz, H-2), 8.01 (s, H-7).

$^{13}\text{C-NMR}$ ($\text{Me}_2\text{SO-d}_6$): δ = 37.0 (C-2'), 55.1 (2 OCH_3), 63.8
 (C-5'), 83.0, 84.2, 85.6, 86.0 (C-1', C-3', C-4', OCDMT),
 10 101.8 (C-3), 106.3 (C-7), 123.1 (C-3a), 128.9 (C-2),
 140.1 (C-6), 140.6 (C-4), 142.4 (C-7a), 193.8 ($\text{C}=\text{S}$).

Analysis for $\text{C}_{40}\text{H}_{34}\text{Cl}_2\text{N}_2\text{O}_6\text{S}$

calc. : C 64.78, H 4.62, Cl 9.55, N 3.77, S 4.32

found : 64.66, 4.59, 9.65, 3.70, 4.40

15 c) 4,6-Dichloro-1-(2',3'-didesoxy- β -D-glyceropento-
furanosyl)-5'-O-(4,4'-dimethoxytrityl)-1H-pyrrolo-
[3,2-c]pyridine.

170 mg. (0.23 mMole) of the compound of Example
 20 b) and 15 mg. (0.1 mMole) 2,2'-azo-bis-(2-methyl)-
 20 propionitrile are dissolved in 10 ml. dry toluene under
 an atmosphere of argon. 140 μl . (0.51 mMole) tri-n-butyl
 stannane are added thereto, while stirring, and the
 reaction mixture is then further stirred for 3 hours at
 80°C. The solvent is removed under a vacuum and the
 25 residue chromatographed on silica gel (elution agent
 dichloromethane). From the main fraction are isolated
 115 mg. (85% of theory) of the desired product.

¹H-NMR (Me₂SO-d₆): δ = 2.05 (H-3'), 2.50 (H-2', superimposed by signals of the solvent), 2.90 - 3.15 (m, H-5'), 4.25 (m, H-4'), 6.38 (m, H-1'), 6.63 (d, J = 3.4 Hz, H-3), 6.69 - 7.30 (aromat. H), 7.79 (d, J = 3.4 Hz, H-2), 7.89 (s, H-7).

d) 2,6-Dichloro-3,7-didesaza-2',3'-didesoxy-9-β-D-ribofuranosylpurine.

The dimethoxytrityl protective group is removed from the compound of Example 20c) analogously to Example 24f).

e) 6-Amino-3,7-didesaza-2',3'-didesoxy-9-β-D-ribofuranosylpurine.

The compound of Example 20d) is treated with hydrazine and subsequently reduced with Raney nickel in the manner described in Example 18c). There is thus obtained the compound described in Example 1d).

f) 3,7-Didesaza-2',3'-didesoxy-9-β-D-ribofuranosylpurine.

The compound of Example 20d) is hydrogenated in the presence of palladium/animal charcoal/hydrogen analogously to Example 24g). There is obtained the compound already described in Example 1A).

g) 3,7-Didesaza-2',3'-didesoxy-9-β-D-ribofuranosylpurin-6-one.

The compound of Example 20d) is treated with an aqueous solution of sodium hydroxide in the manner described in Example 19a) and subsequently hydrogenated

in the manner described in Example 19b). There is thus obtained the compound already described in Example 1E).

Example 21.

5 2-Amino-(2',3'-didesoxy- β -D-glyceropentofuranosyl)-
1H-pyrazolo[3,4-d]pyrimidin-4-one.

This compound is prepared analogously to the method described in Example 17 via 2-amino-(2'-desoxy-9- β -D-ribofuranosyl)-1H-pyrazolo[3,4-d]pyrimidin-4-one and Barton deoxygenation of 2-amino-(2'-desoxy-3'-O-methoxy-
10 thiocarbonyl-5'-toluoylribofuranosyl)-1H-pyrazolo-
[3,4-d]pyrimidin-4-one; m.p. 221°C.

Analysis for $C_{10}H_{13}H_5O_3$ (M.W. 251.25)

calc. : C 47.81, H 5.22, N 27.88

found : 48.01, 5.30, 27.83

15 ^{13}C -NMR (DMSO- d_6): δ = 135.1 (C-3), 99.7 (C-3a), 157.9
(C-4), 155.3 (C-6), 154.5 (C-7a), 83.8 (C-1'), 30.3
(C-2'), 27.3 (C-3'), 81.6 (C-4'), 64.3 (C-5').
 1H -NMR: δ = 6.19 (dd, 1'-H, J = 6.9, 3.5 Hz), 2.06
(m, 3'-H).

20 Example 22.

3,7-Didesaza-2'-desoxy-9- β -D-ribofuranosylpurine
(2'-desoxy-3,7-didesazanebularin)

The compound of Example 18b) is hydrogenated in the presence of palladium/animal charcoal (10% Pd) in
25 ammoniacal methanol. After filtering off the catalyst and evaporating the filtrate in a vacuum, the product is purified from inorganic salts by chromatography on

Amberlite XAD (methanol/water), as well as by crystallisation from water; m.p. 175 - 176°C.

UV (0.1M aqueous hydrochloric acid): $\lambda_{\text{max.}} = 224$,

274 nm

5 ^{13}C -NMR ($[\text{D}_6]\text{DMSO}$): $\delta = 126.9$ (C-2), 101.7 (C-3), 125.5 (C-3a), 143.3 (C-4), 140.6 (C-6), 105.9 (C-7), 139.2 (C-7a), 84.6 (C-1'), 70.8 (C-3'), 87.8 (C-4'), 61.9 (C-5').

10 ^1H -NMR ($\text{DMSO}-d_6$): $\delta = 2.23$ (m, 2'-Hb), 2.29 (m, 2'-Ha), 3.55 (m, 5'-H₂), 3.85 (m, 4'-H), 4.38 (m, 3'-H), 4.99 (5'-OH), 5.37 (3'-OH), 6.42 (pt, 1'-H), 6.66 (d, J = 3 Hz, 3H), 7.62 (d, J = 6 Hz, 7-H), 7.71 (d, J = 3 Hz, 2-H), 8.21 (d, J = 6 Hz, 6-H), 8.23 (s, 4-H).

Analysis for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3$

15 calc. : C 61.53, H 6.02, N 11.96
 found : 61.55, 6.12, 12.02

Example 23.

a) 2-Chloro-6-methoxy-3,7-disaza-2'-desoxy-9- β -D-ribofuranosylpurine.

20 The compound of Example 18b) is heated for 40 hours in 1N methanolic sodium methanolate solution. The reaction product is purified on Amberlite XAD by hydrophobic chromatography (methanol/water).

UV (methanol): $\lambda_{\text{max.}} = 271, 280$ nm.

25 Analysis for $\text{C}_{13}\text{H}_{15}\text{ClN}_2\text{O}_4$

 calc. : C 52.27, H 5.06, Cl 11.87, N 9.38
 found : 52.24, 5.14, 12.05, 9.46

b) 2-Chloro-3,7-didesaza-2'-desoxy-9-β-D-ribo-furanosylpurin-6-one.

Heating the compound of Example 18b) for 30 hours in 2N aqueous sodium hydroxide solution/1,4-dioxan gives the desired compound.

UV (methanol): $\lambda_{\text{max.}} = 262 \text{ nm}$

Analysis for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_4$

calc. : C 59.08, H 6.10, N 10.60

found : 59.09, 6.07, 10.65

$^1\text{H-NMR}$ ($[\text{D}_6]$ DMSO): $\delta = 2.22$ (m, $2'\text{-H}_b$), 2.38 (m, $2'\text{-H}_a$), 3.53 (m, $5'\text{-H}_2$), 3.80 (m, $4'\text{-H}$), 4.33 (m, $3'\text{-H}$), 4.96 ($5'\text{-OH}$), 5.29 ($3'\text{-OH}$), 6.22 (pt, $1'\text{-H}$), 6.54 (d, $J = 3 \text{ Hz}$, 3-H), 6.96 (s, 7-H), 7.38 (d, $J = 3 \text{ Hz}$, 2-H), 11.81 (NH).

Example 24.

a) 4-Chloro-7-(2'-desoxy-3,5-di-O-(p-toluoyl)-β-D-erythro-pentofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine.

1 g. (17.8 mMole) powdered potassium hydroxide is introduced at ambient temperature into 60 ml. dry acetonitrile. 100 μl . (0.31 mMole) tris-[2-(2-methoxyethoxy)-ethyl]-amine are added thereto, while stirring. After 5 minutes, 1.23 g. (8.01 mMole) 4-chloro-7H-pyrrolo[2,3-d]pyrimidine are dissolved in the reaction mixture which is stirred for a further 5 minutes. α -Chloro-2-desoxy-3,5-di-O-p-toluoyl-β-D-erythro-pentofuranose is then added thereto. After stirring for 15 minutes, insoluble material is removed by filtration.

The filtrate is evaporated to dryness in a vacuum and the residue chromatographed on a silica gel column (5 x 7 cm., chloroform). After evaporation of the eluate in a vacuum there are obtained 3.26 g. (81% of theory) of product which crystallises from ethanol in the form of colourless needles; m.p. 120°C.

Further variants of the process of preparation:

(I) Solid-liquid glycosilation in the absence of a catalyst. The reaction is carried out as described above but without the use of a catalyst. After working up, there are obtained 2.82 g. (70% of theory) of the product.

(II) By liquid-liquid phase transfer glycosilation: 500 mg. (3.26 mMole) 4-chloro-7H-pyrrolo[2,3-d]-pyrimidine are dissolved in 20 ml. dichloromethane. 9 ml. of 50% aqueous sodium hydroxide solution are added thereto. After the addition of 10 mg. (0.03 mMole) tetrabutylammonium hydrogen sulphate, the solution is stirred for 1 minute with a vibratory mixer. Subsequently, 1.4 g. (3.61 mMole) of the above-described halogenose is added thereto and mixing continued for a further 3 minutes, whereafter the phases are separated. The aqueous phase is extracted twice with, in each case, 25 ml. dichloromethane. The combined organic phases are dried over anhydrous sodium sulphate. The filtrate is evaporated to dryness and the residue is chromatographed on silica gel (column 5 x 5 cm., chloroform).

Isolation of the product from the main fraction and crystallisation from ethanol gives 1.04 g. (63% of theory) of the desired product; m.p. 118°C.

TLC (cyclohexane/ethyl acetate 3:2 v/v): $R_f = 0.7$.

5 UV (methanol): $\lambda_{\max.} = 240 \text{ nm}$ ($\log \epsilon = 4.48$).

$^1\text{H-NMR}$ (DMSO- d_6): $\delta = 2.37, 2.40$ (s, 2 CH_3), 2.77 (m, 2'- H_b), 3.18 (m, 2'- H_a), 4.60 (m, 4'-H and 5'-H), 5.77 (m, 3'-H), 6.75 (d, $J = 3.7 \text{ Hz}$, 5-H), 6.78 (m, 1'-H), 7.34, 7.91 (m, 8 aromat. H and 6-H), 8.65 (s, 2-H).

10 b) 4-Chloro-7-(2'-desoxy- β -D-erythro-pentofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine.

2.4 g. (4.7 mMole) of the compound of Example 24a) are stirred for 24 hours at ambient temperature in 100 ml. methanol saturated with ammonia. The solution
15 is evaporated to dryness, the residue is adsorbed on 10 g. silica gel 60 H and applied to a silica gel column (4 x 10 cm., chloroform/methanol 95:5 v/v). The product is isolated from the main fraction as a colourless, solid substance which crystallises from ethyl acetate as
20 colourless needles. Yield 1.07 g. (84% of theory); m.p. 162°C.

TLC (chloroform/methanol, 9:1 v/v): $R_f = 0.6$.

UV (methanol): $\lambda_{\max.} = 273 \text{ nm}$ ($\log \epsilon = 3.69$).

$^1\text{H-NMR}$ (DMSO- d_6): $\delta = 2.28$ (m, 2'- H_b), 2.58 (m, 2'- H_a),
25 3.57 (m, 5'-H), 3.87 (m, 4'-H), 4.40 (m, 3'-H), 5.00 (t, $J = 5.4 \text{ Hz}$, 5'-OH), 5.35 (d, $J = 4.2 \text{ Hz}$, 3'-OH), 6.66 (m, 1'-H), 6.72 (d, $J = 3.8 \text{ Hz}$, 5-H), 7.99 (d, $J = 3.8 \text{ Hz}$, 6-H), 8.66 (s, 2-H).

c) 4-Chloro-7-(2'-desoxy- β -D-erythro-pentofuranosyl)-5'-O-(4,4'-dimethoxytrityl)-7H-pyrrolo[2.3-d]-pyrimidine.

1 g. (3.7 mMole) of the compound of Example 24b) is dried by evaporating with 10 ml. dry pyridine. The material is dissolved in 20 ml. dry pyridine. 2 ml. (11.7 mMole) Hünig's base and 2 g. (5.9 mMole) 4,4'-dimethoxytrityl chloride are added thereto. The solution is stirred for 3 hours at ambient temperature. After the addition of 80 ml. 5% aqueous sodium bicarbonate solution, the solution is extracted three times with 100 ml. amounts of dichloromethane. The combined organic phases are dried over anhydrous sodium sulphate. After filtering off, the filtrate is evaporated in a vacuum. The residue is purified by column chromatography (silica gel, elution agent dichloromethane and dichloromethane/ethyl acetate 9:1 v/v). Isolation of the product from the main fraction, dissolving in diethyl ether and precipitation with petroleum ether gives 1.66 g. (78% of theory) of the desired product in the form of a yellowish amorphous substance.

Analysis for $C_{32}H_{30}N_3O_5Cl$ (M.W. 572.1)

calc. : C 67.19, H 5.29, Cl 6.20, N 7.35

found : 67.03, 5.47, 6.19 7.29

25 TLC (dichloromethane/acetone 9:1 v/v): $R_f = 0.3$.

UV (methanol): $\lambda_{max.} = 274 \text{ nm}$ ($\log \epsilon = 3.85$).

$^1\text{H-NMR}$ (DMSO-d_6): = 2.36 (m, 2'-H_b), 2.70 (m, 2'-H_a),
 3.72 (s, OCH₃), 3.18 (d, J = 4.5 Hz, 5'-H), 3.99 (m,
 4'-H), 4.45 (m, 3'-H), 5.42 (d, J = 4.6 Hz, 3'-OH),
 6.65 (m, 1'-H), 6.69 (d, J = 3.7 Hz, 5-H), 7.81 (d,
 5 J = 3.7 Hz, 6-H), 8.64 (s, 2-H).

d) 4-Chloro-7-(2'-desoxy- β -D-erythro-pentofuranosyl)-
5'-O-(4,4'-dimethoxytrityl)-3'-O-phenoxythiocarbonyl-
7H-pyrrolo[2,3-d]pyrimidine.

1 g. (1.7 mMole) of the compound of Example 24c)
 10 is dissolved in 30 ml. dry acetonitrile, 500 mg. (4.1
 mMole) 4-dimethylaminopyridine and 400 μl . (2.9 mMole)
 phenyl chlorothiocarbonate are added thereto and the
 solution is stirred for 16 hours at ambient temperature.
 Subsequently, the reaction mixture is evaporated to dry-
 15 ness in a vacuum and the residue applied to a silica gel
 column (3 x 15 cm., dichloromethane). From the main
 fraction, there are isolated 950 mg. (76% of theory) of
 colourless, amorphous product.

Analysis for $\text{C}_{39}\text{H}_{34}\text{ClN}_3\text{O}_6\text{S}$ (M.W. 708.2)

20 calc. : C 66.14, H 4.84, Cl 5.01, N 5.93, S 4.53
 found : 66.22, 4.94, 5.12, 5.93, 4.46
 TLC (dichloromethane/acetone 95:5 v/v): R_f = 0.8.
 UV (methanol): $\lambda_{\text{max.}}$ = 274 nm ($\log \epsilon$ = 3.87).

$^1\text{H-NMR}$ (DMSO-d_6): δ = 2.84 (m, 2'-H_b), 3.21 (m, 2'-H_a),
 25 3.37 (m, 5'-H), 4.46 (m, 4'-H), 5.92 (m, 3'-H), 6.70
 (m, 1'-H), 6.76 (d, J = 3.8 Hz, 5-H), 7.85 (d, J =
 3.8 Hz, 6-H), 8.61 (s, 2-H).

e) 4-Chloro-7-(2',3'-didesoxy-β-D-glyceropento-furanosyl)-5'-O-(4,4'-dimethoxytrityl)-7H-pyrrolo-[2,3-d]pyrimidine.

800 mg. (1.1 mMole) of the compound of Example 24d) and 40 mg. (0.2 mMole) 2,2'-azo-bis-(2-methyl)-propionitrile are dissolved in 40 ml. dry toluene under an atmosphere of argon. 600 μl. (2.2 mMole) tri-n-butyl stannane are added thereto, while stirring, and the reaction is continued for 2 hours at 75°C. The solvent is removed in a vacuum and the residue chromatographed on silica gel (column 15 x 3 cm., dichloromethane/ethyl acetate 95:5 v/v). From the main fraction, there are obtained 470 mg. (75% of theory) of the desired product. Analysis for C₃₂H₃₀ClN₃O₄ (M.W. 556.1)

15 calc. : C 69.12, H 5.44, Cl 6.38, N 7.56
 found : 69.07, 5.53, 6.33, 7.58

TLC (dichloromethane/acetone 95:5 v/v): R_f = 0.5.

UV (methanol): λ_{max.} = 273 nm (log ε = 3.78).

¹H-NMR (DMSO-d₆): δ = 2.08 (m, 3'-H), 2.10 (m, 2'-H_b),
20 2.43 (m, 2'-H_a), 3.11 (d, J = 4.4 Hz, 5'-H), 3.71 (s, OCH₃), 4.27 (m, 4'-H), 6.55 (dd, J = 3.6 and 6.9 Hz, 1'-H), 6.64 (d, J = 3.7 Hz, 5-H), 7.83 (d, J = 3.7 Hz, 6-H), 8.67 (s, 2-H).

25 f) 4-Chloro-7-(2',3'-didesoxy-β-D-glyceropento-furanosyl)-7H-pyrrolo[2,3-d]pyrimidine.

400 mg. (0.7 mMole) of the compound of Example 24 e) are dissolved in 15 ml. 80% aqueous acetic acid and

stirred for 30 minutes at ambient temperature. The solvent is removed in a vacuum and traces of acetic acid are removed by evaporation with water. The residue is purified by column chromatography (dichloromethane and dichloromethane/methanol, 98:2 v/v). From the main fraction there are obtained 120 mg. (67% of theory) of product which, after crystallisation from ethyl acetate, is obtained in the form of colourless needles; m.p. 90°C.

10 Analysis for $C_{11}H_{12}ClN_3O_2$ (M.W. 253.7)

calc. : C 52.08, H 4.77, Cl 13.98, N 16.56

found : 52.20, 4.81, 14.04, 16.54

TLC (dichloromethane/methanol 95:5 v/v): $R_f = 0.5$.

UV (methanol): $\lambda_{max.} = 274 \text{ nm}$ ($\log \epsilon = 3.65$).

15 $^1\text{H-NMR}$ (DMSO- d_6): $\delta = 2.04$ (m, 3'-H), 2.28 (m, 2'-H_b), 2.46 (m, 2'-H_a), 3.57 (m, 5'-H), 4.11 (m, 4'-H), 4.95 (t, $J = 5.5 \text{ Hz}$, 5'-OH), 6.52 (dd, $J = 3.8$ and 6.9 Hz , 1'-H), 6.69 (d, $J = 3.8 \text{ Hz}$, 5-H), 8.01 (d, $J = 3.8 \text{ Hz}$, 6-H), 8.64 (s, 2-H).

20 g) 7-(2',3'-Dideoxy- β -D-glyceropentofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine.

A solution of 200 mg. (0.8 mMole) of the compound of Example 24f) in 20 ml. methanol, to which had been added 0.5 ml. (6.6 mMole) of concentrated aqueous ammonia solution, is stirred with palladium on animal charcoal (40 mg., 10% Pd) in an atmosphere of hydrogen at ambient temperature for 3 hours. The catalyst is filtered off

and the solvent removed in a vacuum. The residue is dissolved in water and chromatographed on an Amberlite XAD-4 column (1st elution agent water, 2nd elution agent water/methanol 8:2 v/v). Isolation of the product from the main zone gives 130 mg. (75% of theory) of the colourless product in the form of needles; m.p. 131°C. Analysis for $C_{11}H_{13}O_2N_3$ (M.W. 219.2)

calc. : C 60.26, H 5.98, N 19.17

found : 60.19, 5.97, 19.18

10 TLC (dichloromethane/methanol 9:1 v/v): $R_f = 0.6$.

UV (methanol): $\lambda_{max.} = 270 \text{ nm}$ ($\log \epsilon = 3.56$).

$^1\text{H-NMR}$ (DMSO- d_6): $\delta = 2.06$ (m, 3'-H), 2.27 (m, 2'-H_b), 2.42 (m, 2'-H_a), 3.55 (m, 5'-H), 4.09 (m, 4'-H), 4.93 (t, $J = 5.5 \text{ Hz}$, 5'-OH), 6.54 (dd, $J = 4.3$ and 6.9 Hz , 1'-H), 6.67 (d, $J = 3.7 \text{ Hz}$, 5-H), 7.86 (d, $J = 3.7 \text{ Hz}$, 6-H), 8.79 (s, 4-H), 9.01 (s, 2-H).

h) 4-Amino-7-(2',3'-dideoxy- β -D-glyceropentofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine (2',3'-dideoxy-tubercidin)

20 200 mg. (0.8 mMole) of the compound of Example 24f) are stirred in 60 ml. 25% aqueous ammonia solution for 15 hours at 100°C. under pressure in a steel bomb. The solvent is subsequently removed in a vacuum and the residue dissolved in 200 ml. water. This solution is purified on Dowex 1 x 2 (OH⁻ form). The column is washed with water and the product eluted with water/methanol (9:1 v/v). From the main zone are obtained

120 mg. (65% of theory) of product.

TLC (dichloromethane/methanol 9:1 v/v): $R_f = 0.3$.

$^1\text{H-NMR}$ (DMSO-d_6): $\delta = 2.03$ (m, 3'-H), 2.22 (m, 2'-H_a),
2.33 (m, 2'-H_b), 3.53 (m, 5'-H), 4.04 (m, 4'-H), 4.99
5 (m, 5'-OH), 6.35 (m, 1'-H), 6.51 (d, $J = 3.6$ Hz, 5-H),
7.00 (s, NH_2), 7.34 (d, $J = 3.6$ Hz, 6-H), 8.04 (s, 2-H).

i) 7-(2',3'-Didesoxy- β -D-glyceropentofuranosyl)-4-methoxy-7H-pyrrolo[2,3-d]pyrimidine.

170 mg. (0.7 mMole) of the compound of Example 24f)
10 are dissolved in 5 ml. 1M methanolic methanolate solution
and stirred at ambient temperature for 4 hours. The
solution is neutralised with 80% acetic acid, evaporated
in a vacuum and the residue applied to a silica gel
column (elution agent dichloromethane/methanol 98:2 v/v).
15 Isolation of the main zone gives a colourless oil which,
upon storing, crystallises in the form of needles.
Yield 130 mg. (78% of theory).

j) 7-(2',3'-Didesoxy- β -D-glyceropentofuranosyl)-4H-pyrrolo[2,3-d]pyrimidin-4-one.

20 200 mg. (0.8 mMole) of the compound of Example
24f) are suspended in 10 ml. 2N aqueous sodium hydroxide
solution and boiled under reflux for 5 hours. The
solution is neutralised with 80% acetic acid and the
insoluble material is removed by filtration. The
25 filtrate is applied to an Amberlite XAD-4 column. The
column is washed with 500 ml. of water and the product
eluted with water/isopropanol (9:1 v/v). There are

obtained 180 mg. (80% of theory) of product.

Example 25.

1-(2',3'-Dideoxy- β -D-glyceropentafuranosyl)-1H-pyrazolo[3.4-d]pyrimidin-4-one.

5 The product of Example 17d) is deaminated with adenosine deaminase from intestinal calf mucosa cells. The progress of the reaction is monitored UV spectroscopically at 275 nm. The reaction gives the product quantitatively in the form of colourless crystals;

10 m.p. 171°C.

UV (methanol): $\lambda_{\text{max.}}$ = 251 nm (ϵ = 7700).

TLC (silica gel, dichloromethane/methanol 9:1 v/v):

R_f = 0.5.

15 ^{13}C -NMR ($[\text{D}_6]$ DMSO): δ = 135.2 (C-8), 106.1 (C-5), 157.3 (C-6), 148.4 (C-2), 152.3 (C-4), 84.6 (C-1'), 30.7 (C-2'), 27.3 (C-3'), 82.2 (C-4'), 64.2 (C-5').

^1H -NMR ($[\text{D}_6]$ DMSO): δ = 2.13 (m, 3'-H), 2.40 (m, 2'-H), 3.40 (m, 5'-H), 4.09 (m, 4'-H), 4.73 (m, 5'-OH), 6.43 (m, 1'-H), 8.11 (s, 3-H), 8.13 (s, 6-H).

20 Example 26.

2-Amino-7-desaza-2',3'-dideoxy-9- β -D-ribofuranosyl-purin-6-one 5'-triphosphate.

Analysis for $\text{C}_{11}\text{H}_{14}\text{H}_4\text{O}_{12}\text{P}_3\text{Na}_3$ (M.W. 556.2)

calc. : P 16.7

25 found : 16.4

UV (buffer, pH 7.0): $\lambda_{\text{max.}}$ = 259 nm (ϵ = 13400)

-60-

^{31}P -NMR (D_2O): $\delta = -8.35$ (d, P- γ), -10.0 (d, P- α),
 -21.5 (t, P- β).

Example 27.

2-Amino-3,7-didesaza-2'-desoxy-9- β -D-ribofuranosyl-
 5 purin-6-one 5'-triphosphate.

Analysis for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_{13}\text{P}_3\text{Na}_3$ (M.W. 555.2)

calc. : P 16.75

found : 16.5

UV (buffer, pH 7.0): $\lambda_{\text{max.}} = 272$ nm ($\epsilon = 12400$).

10 Example 28.

3,7-Didesaza-2',3'-didesoxy-9- β -D-ribofuranosylpurine
5'-triphosphate.

Analysis for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_{11}\text{P}_3\text{Na}_3$ (M.W. 524.1)

calc. : P 17.7

15 found : 17.3

UV (buffer, pH 7.0): $\lambda_{\text{max.}} = 224, 274$ nm.

All of the triphosphates described in Examples
 26 to 28 are prepared by phosphorylation of the corres-
 ponding nucleosides by the method described by

20 Yoshikawa (Tetrahedron Letters, 50, 5065/1967) to give
 the 5'-monophosphates and subsequent conversion into the
 5'-triphosphates by the method of Hoard and Ott
 (J.A.C.S., 87, 1785/1965).

Example 29.25 Antiviral activity.

The stability of the N-glycosidic bond of 2',3'-
 didesoxynucleosides is bound up with the antiviral

activity.

The hydrolysis of the bond was investigated at 25°C. in three different concentrations of hydrochloric acid. For this purpose, the UV absorption (E_t) was measured at 258 nm. Via the absorption/time curve, there were determined the velocity constants of the hydrolysis (k) and the half life times ($T/2$) on the basis of the following equation:

$$k = 1/t \times \ln (E_o - E_{oo}) / (E_t - E_{oo})$$

E_o being the absorption at time $t = 0$ and E_{oo} being the absorption after complete termination of the reaction.

There were compared 2',3'-didesoxyadenosine (a) and 6-amino-8-aza-7-desaza-2',3'-didesoxy-9-β-D-ribofuranosylpurine (b) at 25°C. The results obtained are set out in the following Table:

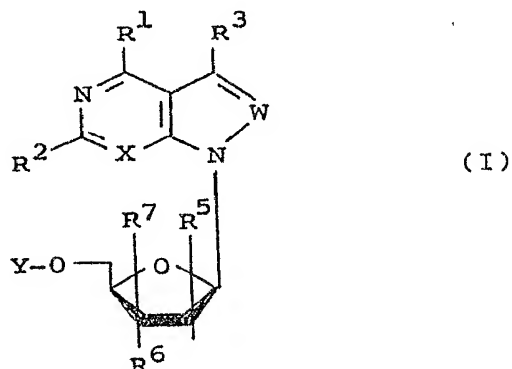
Table

		1N HCl	0.1N HCl	0.01N HCl
20	(a)	T/2 -	1.9 min.	31.5 min.
		k -	0.363 min ⁻¹	0.022 min ⁻¹
	(b)	T/2 0.83 min.	20.4 min.	280 min.
		k 0.85 min ⁻¹	0.033 min ⁻¹	0.0025 min ⁻¹

The above Table shows that the compound (b) according to the present invention is more than 10 times more stable and thus more antivirally effective than (a).

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Desazapurine-nucleoside derivatives of the general formula:-



wherein X is a nitrogen atom or a methine radical; W is a nitrogen atom or a $\text{C}=\text{R}^4$ radical, R^1 , R^2 , R^3 and R^4 , which can be the same or different, are hydrogen or halogen atoms, hydroxyl or mercapto groups, lower alkyl, lower alkylthio, lower alkoxy, aralkyl, aralkoxy, aryloxy, unsubstituted amino, or amino substituted once or twice by $\text{C}_1\text{-C}_5$ alkyl or $\text{C}_1\text{-C}_5$ alkyl substituted once or twice by $\text{C}_1\text{-C}_5$ alkoxy, halogen or amino; R^5 is a hydrogen atom or a hydroxyl group; R^6 and R^7 are each hydrogen atoms or one of them is a halogen atom, cyano or azido, unsubstituted amino, or amino substituted once or twice by $\text{C}_1\text{-C}_5$ alkyl or $\text{C}_1\text{-C}_5$ alkyl substituted once or twice by $\text{C}_1\text{-C}_5$ alkoxy, halogen or amino; and one of R^6 and R^7 can also be a hydroxyl group when X is a methine radical and, in addition R^5 and R^7 can together also

represent a further valency bond between C-2' and C-3'; and Y is a hydrogen atom or a mono-, di- or tri-phosphate group, as well as the tautomers and salts thereof and nucleic acids which contain one or more compounds of general formula (I) as structural components, provided that when X is nitrogen, W is CR⁴, and R¹ is amino, at least one of Y, R², R³, R⁴, R⁵, R⁶ and R⁷ is other than hydrogen;

and provided that when X and W are methine and R¹ and R² are both chlorine and R⁶ is hydroxy at least one of Y, R³, R⁵ and R⁷ is other than hydrogen;

and provided that when X is methine, W is nitrogen, R¹ and R⁶ are hydroxyl and R² is amino, at least one of Y, R³, R⁵ and R⁷ is other than hydrogen.

2. A nucleic acid containing one or more desazapurine nucleoside derivatives of formula (I), as defined in claim 1.

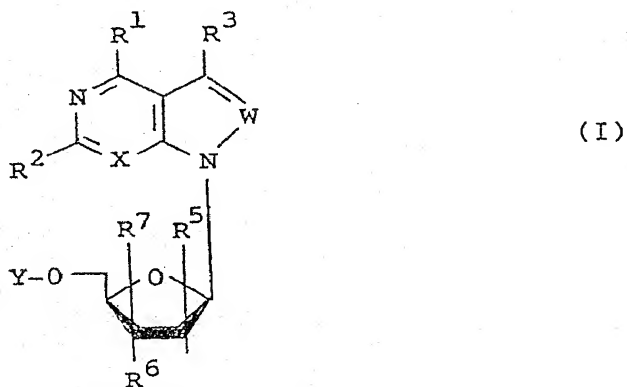
3. A nucleic acid according to claim 2, comprising 2 to 1000 nucleotide structural components.

4. A nucleic acid according to claim 2, comprising 8 to 50 nucleotide structural components.

5. A nucleic acid according to claim 2, comprising 15 to 30 nucleotide structural components.

6. A derivative of claim 1, wherein said aralkyl is benzyl.
7. A derivative of claim 1, wherein said aryloxy radical is phenyloxy.
8. A derivative of claim 1, wherein at least one of R^1 , R^2 , R^3 , R^4 , R^6 and R^7 is amino.
9. A derivative of claim 1, wherein at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is substituted at least once by an alkyl radical with from 1 to 5 carbon atoms.
10. A derivative of claim 1, wherein at least one of R^1 , R^2 , R^3 and R^4 is aralkyl.
11. A derivative of claim 1, wherein X is methine and at least one of R^6 and R^7 is hydroxy.
12. 2-Amino-7-desaza-2',3'-dideoxy-9-beta-D-ribo-furanosyl-purine-6-one.

13. 6-Amino-8-aza-7-desaza-2',3'-didesoxy-9-beta-D-ribofuranosylpurine.
14. 3,7-Didesaza-2',3'-didesoxy-9-beta-D-ribofuranosyl-purine-6-one.
15. 7-(2',3'-Didesoxy-beta-D-glyceropentofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine.
16. 4-Amino-7-(2',3'-didesoxy-beta-D-glyceropentofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine.
17. A pharmaceutical composition comprising at least one compound of formula I



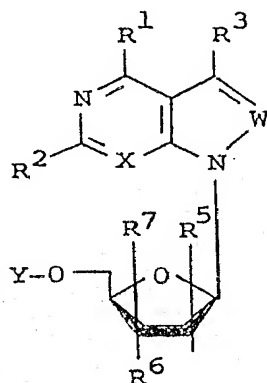
wherein X is a nitrogen atom or a methine radical; W is a nitrogen atom or a $\equiv\text{C}-\text{R}^4$ radical; R^1 , R^2 , R^3 , and R^4 , which can be the same or different, are hydrogen

or halogen atoms, hydroxyl or mercapto groups, lower alkyl, lower alkylthio, lower alkoxy, aralkyl, aralkoxy, aryloxy, unsubstituted amino, or amino substituted once or twice by C_1-C_5 alkyl or C_1-C_5 alkyl substituted once or twice by C_1-C_5 alkoxy, halogen or amino; R^5 is a hydrogen atom or a hydroxyl group; R^6 and R^7 are each hydrogen atoms or one of them is a halogen atom, cyano or azido, unsubstituted amino, or amino substituted once or twice by C_1-C_5 alkyl or C_1-C_5 alkyl substituted once or twice by C_1-C_5 alkoxy, halogen or amino, and one of R^6 and R^7 can also be a hydroxyl group when X is a methine radical and, in addition R^5 and R^7 can together also represent a further valency bond between C-2' and C-3'; and Y is a hydrogen atom or a mono-, di- or tri-phosphate group, or a tautomer thereof, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, provided that when X is nitrogen, W is CR^4 , and R^1 is amino, at least one of Y, R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is other than hydrogen;

and provided that when X and W are methine and R^1 and R^2 are both chlorine and R^6 is hydroxy at least one of Y, R^3 , R^5 and R^7 is other than hydrogen;

and provided that when X is methine, W is nitrogen, R^1 and R^6 are hydroxyl and R^2 is amino, at least one of Y, R^3 , R^5 and R^7 is other than hydrogen in association with a pharmaceutically acceptable carrier.

18. An antiviral pharmaceutical composition comprising an acceptable, effective antiviral amount of a desazapurine-nucleoside derivative of formula (I)



(I)

wherein X is a nitrogen atom or a methine radical; W is a nitrogen atom or a $\text{C}=\text{R}^4$ radical; R^1 , R^2 , R^3 and R^4 , which can be the same or different, are hydrogen or halogen atoms, hydroxyl or mercapto groups, lower alkyl, lower alkylthio, lower alkoxy, aralkyl, aralkoxy, aryloxy, unsubstituted amino, or amino substituted once or twice by C_1-C_5 alkyl or C_1-C_5 alkyl substituted once or twice by C_1-C_5 alkoxy,

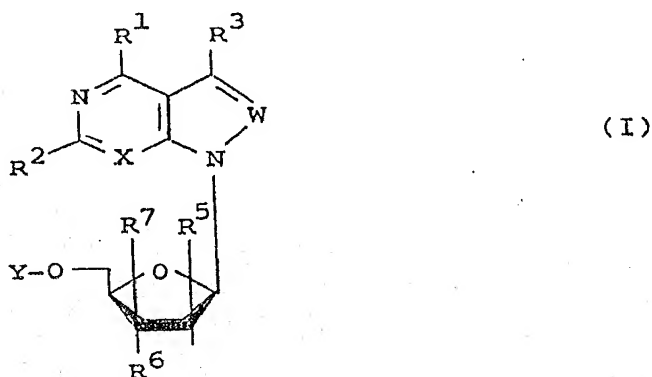
halogen or amino; R^5 is a hydrogen atom or a hydroxyl group; R^6 and R^7 are each hydrogen atoms or one of them is a halogen atom, cyano or azido, unsubstituted amino, or amino substituted once or twice by C_1-C_5 alkyl or C_1-C_5 alkyl substituted once or twice by C_1-C_5 alkoxy, halogen or amino; and one of R^6 and R^7 can also be a hydroxyl group when X is a methine radical and, in addition R^5 and R^7 can together also represent a further valency bond between C-2' and C-3'; and Y is a hydrogen atom or a mono-, di- or tri-phosphate group, or a tautomer thereof, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, provided that when X is nitrogen, W is CR^4 , and R^1 is amino, at least one of Y, R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is other than hydrogen;

and provided that when X and W are methine and R^1 and R^2 are both chlorine and R^6 is hydroxy at least one of Y, R^3 , R^5 and R^7 is other than hydrogen;

and provided that when X is methine, W is nitrogen, R^1 and R^6 are hydroxyl and R^2 is amino, at least one of Y, R^3 , R^5 and R^7 is other than hydrogen in association with a pharmaceutically acceptable carrier therefor.

19. A composition according to claim 18 containing an amount of said derivative (I), or salt thereof, effective to inhibit reverse transcriptase.

20. In a method of DNA sequencing according to Sanger's method, the improvement in which there is employed a derivative of formula (I)



wherein X is a methine radical,

W is a nitrogen atom or a $\text{C}=\text{R}^4$ radical; R^1 , R^2 , R^3 and R^4 , which can be the same or different, are hydrogen or halogen atoms, hydroxyl or mercapto groups, lower alkyl, lower alkylthio, lower alkoxy, aralkyl, aralkoxy, aryloxy, unsubstituted amino, or amino substituted once or twice by $\text{C}_1\text{-C}_5$ alkyl or

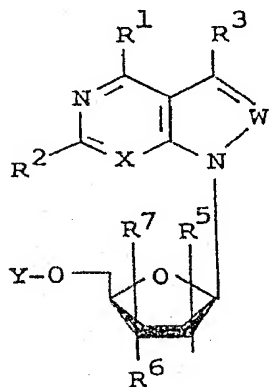
C₁-C₅ alkyl substituted once or twice by C₁-C₅ alkoxy, halogen or amino; R⁵ is a hydrogen atom or a hydroxyl group;

R⁶ is hydroxyl;

R⁷ is a hydrogen atom, halogen atom, cyano, azido, unsubstituted amino, or amino substituted once or twice by C₁-C₅ alkyl or C₁-C₅ alkyl substituted once or twice by C₁-C₅ alkoxy, halogen or amino; or

R⁵ and R⁷ together represent a further valency bond between C-2' and C-3'; and Y is a hydrogen atom or a mono-, di- or tri-phosphate group, or a tautomer thereof.

21. In a method of DNA sequencing employing a chain terminator in accordance with Sanger's method, the improvement in which the chain terminator is a derivative of formula (I)



(I)

wherein X is a nitrogen atom or a methine radical;

W is a nitrogen atom or a $\text{C}=\text{C}-\text{R}^4$ radical; R^1 , R^2 , R^3 and R^4 , which can be the same or different, are hydrogen or halogen atoms, hydroxyl or mercapto groups, lower alkyl, lower alkylthio, lower alkoxy, aralkyl, aralkoxy, aryloxy, unsubstituted amino, or amino substituted once or twice by $\text{C}_1\text{-C}_5$ alkyl or $\text{C}_1\text{-C}_5$ alkyl substituted once or twice by $\text{C}_1\text{-C}_5$ alkoxy, halogen or amino; R^5 is a hydrogen atom or a hydroxyl group;

R^6 and R^7 are both hydrogen atoms; and Y is a hydrogen atom or a mono-, di- or tri-phosphate group, or a tautomer thereof, in which R^6 and R^7 are hydrogen atoms.

22. A desazapurine-nucleoside derivative of formula (I), as defined in claim 1, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, or a tautomer thereof, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, for use in the inhibition of the enzyme reverse transcriptase.

23. Use of a desazapurine-nucleoside derivative of formula (I), as defined in claim 1, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, or a tautomer thereof, or a

pharmaceutically acceptable, pharmacologically compatible salt thereof, for the manufacture of a medicament for the treatment of virus infections.

24. Use of a desazapurine-nucleoside derivative of formula (I), as defined in claim 1, 6, 7 or 10, wherein R^6 is a hydroxyl group and W is a methine radical, or a tautomer thereof, for DNA sequencing according to Sanger's method.

25. Use of a desazapurine-nucleoside derivative of formula (I), as defined in claim 1, 6, 7 or 10, in which R^6 and R^7 are hydrogen atoms, or a tautomer thereof, for DNA sequencing according to Sanger's method.

26. A pharmaceutical composition comprising an effectively acceptable amount of a derivative defined in claim 6, 7, 8, 9, 10 or 11, or a tautomer thereof, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, in association with a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising an effective, acceptable amount of a compound of claim 12, 13, 14, 15 or 16, in association with a pharmaceutically acceptable carrier.

28. An antiviral pharmaceutical composition comprising an acceptable, effective antiviral amount of a derivative as defined in claim 6, 7, 8, 9, 10 or 11, or a tautomer thereof, or a pharmaceutically acceptable, pharmacologically compatible salt thereof, in association with a pharmaceutically acceptable carrier.

29. An antiviral pharmaceutical composition comprising an acceptable, effective antiviral amount of a compound of claim 12, 13, 14, 15 or 16, in association with a pharmaceutically acceptable carrier.



SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente